Muscle structure; -function and physical function outcomes in ICU survivors

by
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ABSTRACT

Introduction: The current challenge in critical care medicine is improving outcomes of intensive care unit (ICU) survivors. Many survivors experience long-lasting physical, cognitive, and mental impairments. The aims of this thesis are to 1) explore the current literature reporting on physical function utilising the concepts of post intensive care syndrome and the international classification of function (ICF), and 2) describe a South African (SA) critically ill population admitted to a privately funded hospital.

Method: A scoping review was performed to determine how physical function is assessed in survivors. Papers were selected based on criteria defined through an iterative process. The results of the scoping review informed the development of the primary study. The primary study aimed to describe the baseline characteristics and outcomes of a critically ill population admitted to a privately funded hospital in SA. The peripheral and respiratory muscle structure using ultrasonography (US); respiratory and peripheral muscle strength by manual muscle testing, hand held dynamometry (HHD) and maximal inspiratory pressure; respiratory muscle endurance testing; physical function by the Chelsea critical care physical assessment tool (CPAx) and Barthel Index (BI); exercise tolerance by the six-minute walk test (6MWT); and health related quality of life (HRQoL) using the EQ-5D was assessed at different timepoints.

Results: At title level 315 papers were identified and 13 papers were included in the scoping review. No included papers were from developing countries. Studies reporting physical function as activity limitation (n=5) used performance-based measures. Participation restrictions (n=8) were investigated using self-report measures. Relationships were identified between performance-based physical function and factors of the neuromusculoskeletal body system and self-report physical function and mental health impairments. 21 participants were included in the primary study. The median age of the sample was 70 (IQR 59-80) years, and SAPS 3 score was 57 (IQR 43-67). A large number of participants did not demonstrate change in peripheral muscle thickness, but diaphragmatic thickening fraction (DTF) was >30% at all timepoints. Muscle weakness was seen at hospital discharge as median HHD of the lower limb of ≥40% of the predicted norms. Exercise tolerance was 20.8% (SD 18.6) of the predicted normal values. Performance-based physical function (CPAx) was 36.3

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(SD 6.2) at ICU discharge and 41.8 (SD 5.1) at hospital discharge. Self-reported physical function (BI) was 80 (IQR 71-94) and 100 (IQR 95-100) at hospital discharge and three months. The HRQoL domains that had the highest number of participants demonstrating slight to severe problems at three months were mobility (n=6 [40%]), usual activities (n=5 [33%]) and pain (n=7 [47%]).

Conclusion: Physical function is being evaluated in ICU survivors. However, the number of articles reporting on physical function as both activity limitation and participation restriction are limited. Physical function is a complex outcome. The one-dimensional approach reported in current literature needs attention. Critically ill patients admitted to a privately funded hospital were older and more severely ill than previously documented cohorts from the public sector in SA. Exercise tolerance and muscle strength, were decreased at hospital discharge when compared to reference values. At three months the HRQoL measure revealed continuing problems.

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OPSOMMING

Inleiding: Die huidige uitdaging in kritiekesorg medisyne is om die uitkomste van intensiewe sorgeenheid (ISE) oorlewendes te verbeter. Baie oorlewendes ervaar langdurige liggaamlike, kognitiewe en geestelike beperkings. Die doel van hierdie tesis is om 1) die huidige literatuur oor fisiesies funksie te ondersoek deur gebruik te maak van die konsepte van post-intensiewe sorg sindroom en die internasionale klassifikasie van funksie (ICF), en 2) 'n Suid-Afrikaanse (SA) kritiek-siek bevolking te beskryf wat toegelaat is tot 'n privaat gefinansierde hospitaal.

Metode: 'n Omvangsbepaling is uitgevoer om vas te stel hoe fisiese funksie by oorlewendes geassesseer word. Artikels is gekies op grond van kriteria bepaal deur 'n iteratiewe proses. Die resultate van die omvangsbepaling het die ontwikkeling van die primêre studie beïnvloed. Die primêre studie het ten doel gehad om die basiese eienskappe en uitkomste van 'n kritiek-siek bevolking wat in 'n privaat hospitaal in SA opgeneem is, te beskryf. Die perifere en respiratoriese spierstruktuur deur ultrasonografie (VS); respiratoriese en perifere spierkrag deur manuele spiertoetsing, hand toestel dinamometrie (HHD) en maksimale inspiratoriese druk; uithouvermoë van respiratoriese spiere; fisiese funksie deur die Chelsea fisiese assessering vir kritieke sorg (CPAx) en Barthel Indeks (BI); oefening-uithouvermoë deur die ses minute stap toets (6MWT); en gesondheidsverwante lewenskwaliteit (HRQoL) met behulp van die EQ-5D is op verskillende tydspunte geassesseer.

Resultate: Op titelvlak is 315 artikels geïdentifiseer en 13 is artikels ingesluit by die bestekopname. Geen artikels was van ontwikkelende lande nie. Studies wat fisiese funksie as aktiwiteitsbeperking rapporteer (n = 5), het prestasiegebaseerde maatstawwe gebruik. Deelnamebeperkings (n = 8) is ondersoek met behulp van selfgeraporteerde maatstawwe. Verwantskappe is geïdentifiseer tussen prestasiegebaseerde fisiese funksie en faktore van die neuromuskuloskeletale liggaamstelsel en geestes siektes en selfgeraporteerde fisiese funksie. 21 deelnemers is in die primêre studie ingesluit. Die mediaan ouderdom van die groep was 70 (IQR 59-80) jaar, en die SAPS 3-telling was 57 (IQR 43-67). 'n Groot aantal deelnemers het geen verandering in perifere spierdikte getoon nie, maar die diafragmatiese verdikkingsfraksie (DTF) was te alle tye >30%. Spierswakheid is gesien tydens

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hospitaal ontslag as 'n mediaan HHD van die onderste ledemaat ≥40% van die voorspelde norme. Oefening-uithouvermoë was 20,8% (SD 18,6) van die voorspelde norme. Prestasiegebaseerde fisieke funksie (CPAx) was 36.3 (SD 6.2) met ISE ontslag en 41.8 (SD 5.1) met hospitaal ontslag. Selfgerapporteerde fisiese funksie (BI) was mediaan 80 (IQR 71-94) en 100 (IQR 95-100) by ontslag vanaf hospitaal en drie maande. Die HRQoL-domeine wat na drie maande die meeste deelnemers gehad het wat effens tot ernstige probleme gedemonstreet het, is mobiliteit (n = 6 [40%]), gewone aktiwiteite (n = 5 [33%]) en pyn (n = 7 [47%]).

Gevolgtrekking: Fisiese funksie word geëvalueer by ISE-oorlewendes. Die aantal artikels wat oor fisieke funksies verslag doen as beide aktiwiteitsbeperking en deelnamebeperkings is beperk. Fisiese funksie is 'n ingewikkelde uitkoms. Die eendimensionele benadering in die huidige literatuur, moet aandag geniet. Die kritiek-siek pasiënte, was ouer en ernstiger siek as voorheen gedokumenteerde groepe van die openbare sektor in SA. Oefenings-uithouvermoë en spierkrag was verlaag in vergelyking met verwysingswaardes. Op drie maande het die HRQoL-maatstaf voortdurende probleme aan die lig gebring.

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"For from Him and through Him and to Him are all things. To Him be the glory and honour forever! Amen." – Romans 11:36

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GLOSSARY OF TERMS:

PICS:	New or worsening functional impairments in physical, mental or cognitive function that develop during critical illness and persists after hospital discharge.(1)
PICS Impairment domains:	Physical, cognitive or mental health impairments.(1)
ICF Constructs:	Three levels of impairments in function including body structure and function (physiological functions of body systems or anatomical parts of the body) activity limitations (execution of a task or action) and participation restrictions (problems with involvement in life situations).(2)
COMS:	Minimum collection of outcomes that should be reported in all studies when conducting research within a specific field and serves as a standard to ensure essential outcome assessment.(3)
ICU-AW:	Muscle weakness that develops following the onset of critical illness, meeting specific strength-related criteria, that is identified during physical examination.(1)

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LIST OF ABBREVIATIONS:

6MWD:	six-minute walk distance
6MWT:	six-minute walk test
ADL's:	activities of daily living
ALS:	Alison Lupton-Smith
ASIS:	anterior superior iliac spine
ATS:	American Thoracic Society
BDI-II:	Beck depression inventory
BI:	Barthel Index
CIM:	critical illness myopathy
CIP:	critical illness polyneuropathy
COMS:	core outcome measure set
COPD:	Chronic Obstructive Pulmonary Disease
CPAx:	Chelsea critical care physical assessment tool
CRP:	C-reactive protein
CT:	computed tomography
DM:	Diabetes Mellitus
DTF:	diaphragm thickening fraction
EQ-5D:	EuroQol five dimensions
FHSQ:	functional health status questionnaire
FIM:	functional independence measure
GCS:	Glasgow coma scale
HADS:	hospital anxiety and depression scale
HGT:	blood glucose level
HHD:	handheld dynamometry
HRQoL:	health related quality of life
IADL	Instrumental Acts of Daily Living
ICC:	intraclass correlation coefficient
ICF:	International Classification of Function
ICU-AW:	intensive care unit acquired weakness
ICU:	intensive care unit
IESR:	impact of event scale reviewed
IMS:	ICU mobility scale
Kg:	kilograms
LOS:	length of stay
LOV:	length of ventilation
MIP:	maximal inspiratory pressure
MRC-SS:	Medical Research Council sum score
MRI:	magnetic resonance imaging
MRS:	Modified Rankin scale
NMBA's:	neuromuscular blocking agents
PdTwi:	twitch diaphragmatic pressure

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PI:	primary investigator
PICS:	Post Intensive Care Syndrome
PRISMA_ScR	Prisma Scoping Review
PTSD:	Post-traumatic Stress Disorder
QMLT:	quadriceps muscle layer thickness
RASS:	Richmond agitation and sedation scale
RF:	Rectus Femoris
ROM:	range of motion
SA:	South Africa
SAPS 3:	Simplified Acute Physiology Score 3
SC:	Shanita Chiba
SES:	self-efficacy scale
SF-36 PCS:	36 item short form survey physical component score
Tdi:	diaphragm muscle thickness
US:	ultrasonography/ultrasound
VI:	Vastus Intermedius
VIDD:	ventilator induced diaphragmatic dysfunction
WCC:	white cell count
WHO:	World Health Organization

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CHAPTER 1 : INTRODUCTION

The current challenge in modern critical care medicine is improving the outcome of intensive care unit (ICU) survivors.(4) Improved mortality and increased awareness of morbidity has highlighted this challenge.(5) Currently, many survivors experience a multitude of long-lasting impairments. These include physical, cognitive, and mental deficits.(1,6,7) The term used to describe these new or worsening impairments, that develop following critical illness and persists after hospital discharge, is post intensive care syndrome (PICS).(1) One of the largest health challenges faced by survivors of critical illness is PICS (8)

The long-term impairments of PICS lead to a coexisting decline in physical function,(9,10) health related quality of life (HRQoL),(11) and poor return to work.(12) Poor HRQoL has been demonstrated as long as five years post discharge (13) and substantial impairments in physical function, as long as two years post discharge.(14) The physical domains measured within HRQoL demonstrate the largest deficit, even up to five years post discharge.(13) This decline in physical function and HRQoL has been associated with persistent muscle weakness, known as ICU acquired weakness (ICU-AW).(14)

ICU-AW is described as clinical signs of muscle weakness that develop following the onset of critical illness.(10) The causes, risk factors (such as environmental exposures of critical illness),(4) pattern, and prevalence of muscle weakness remain poorly understood. Environmental exposures such as increased length of stay (LOS) in ICU, prolonged mechanical ventilation,(5,10) and medication exposures,(4) are associated with poorer patient outcomes, specifically mortality rate, physical function, and a higher prevalence of ICU-AW.(4,5)

Parry et al. (15) found that peripheral muscle mass can decrease by as much as 30% within 10 days of ICU stay. A period as short as 18 hours of mechanical ventilation has been found to cause a decrease in diaphragmatic contractile function and caused diaphragmatic atrophy.(16) The damaging effects of prolonged mechanical ventilation on the diaphragm is termed ventilator-induced diaphragmatic dysfunction (VIDD).(16)

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Studies performed on peripheral and respiratory muscles thus demonstrate the rapid way muscles are affected due to critical illness and ICU related environmental exposures.(17–20)

Declines in peripheral and respiratory muscle function have been associated with prolonged hospital and ICU LOS, increased rate of re-admission, and impaired functional status.(21) Impairments in muscle strength have also been associated with secondary complications such as joint contractures, pressure sores and respiratory complications (atelectasis, pneumonia and weaning failure).(21)

Research is increasingly focused on investigating and determining survivor outcomes and their experiences, in an attempt to address the major health challenge of PICS.(3) Unfortunately, in current research, there is considerable variance in the outcomes that are evaluated and how they are investigated, when assessing the post discharge status of critical illness survivors.(3,7,22) This prevents and delays the comparison and synthesis of results across studies and slows advances in research and clinical practice guidelines.(22)

A new approach to address the variance in outcome assessment, is the creation of a core outcome measurement set (COMS).(3,23) A minimum collection of outcomes that should be reported in all studies when conducting research within a specific field.(3,23) This serves as a standard so that crucial outcomes are assessed in the same way (using the same measures), within a given field. (3,23)

A COMS for ICU survivors has been developed.(3) This COMS includes the following domains: physical function, cognitive function, mental health, muscle and/or nerve function, and HRQoL.(3,23) This COMS also addresses the three major impairments (physical, cognitive and mental), identified in PICS.(1)

Context for the impairments in physical, cognitive and mental function within PICS can be provided using the International Classification of Function (ICF) framework.(2) The ICF is a known framework of function that was compiled by the World Health Organization (WHO) in 2002.(2) This framework defines functioning as the interaction between three distinct constructs: physiological assessment (i.e. body structure and

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function), performance-based measurement (i.e. activity limitation) and lastly, assessment of participation (i.e. participation restriction).(2,5)

Limited studies have been reported on the outcomes of the South African (SA) critically ill population. To the best of our knowledge no studies have been performed on the outcomes of peripheral and respiratory muscle structure and function, exercise tolerance, and HRQoL within hospital stay of a SA critically ill population. There have also been limited studies published that report on physical function and HRQoL outcomes.

In SA we have a divide within our healthcare system. One part making use of public health care and the other making use of private health care. The public health care system services 84% of the SA population.(24) However, only 23.2% of public hospitals have ICU and/or high care facilities.(25) In comparison, 84.4% of private hospitals in SA have ICU and/or high care facilities. It is thought that the resources and management of the public and private health care sectors vary widely, along with the baseline characteristics of critically ill populations. Few studies have evaluated these characteristics and physical outcomes of the critically ill populations within SA.

A study performed in a private hospital in the Gauteng province of SA, is the only one known to report on baseline characteristics and outcomes of muscle strength, exercise tolerance, and HRQoL.(26) These outcomes were reported at one- and six-months post discharge, physical function was the only outcome reported on within hospital stay.(26)

Studies performed on the critically ill population within the public health care sector have predominantly investigated outcomes in HRQoL, with one study evaluating physical function in this population.(27) Nonetheless, a decreased HRQoL, particularly in the physical domain, was evident in a population surviving surgical ICU in SA.(28) Trauma survivors in Johannesburg, also showed a decrease in the physical and emotional HRQoL domains at six months post discharge.(29)

The aims of this thesis are to 1) explore the current literature reporting on physical function using the concepts of PICS (1) and the classification of function by the WHO,

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through the ICF (2) and 2) report on baseline characteristics and outcomes of a SA critically ill population.

Following the introduction (Chapter 1) this thesis will be presented in the following five chapters. A scoping review on physical function and related impairments in critical illness survivors (Chapter 2); a methodologic description of the primary research study (Chapter 3); results and statistical analysis of an observational research study on the patient characteristics, critical illness factors and outcomes in an adult critically ill population of SA (Chapter 4); and a discussion, interpretation and contextualisation of the statistical analysis of the primary research study (Chapter 5). Chapter 6 will conclude the primary research study, report on its limitations and make recommendations for future research. Chapter 2 will be submitted to the journal of Critical Care Medicine as a Scoping Review. The search will be updated before submission of the paper. We have included a single reference list for the thesis.

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CHAPTER 2 : LITERATURE REVIEW

This chapter was prepared as a manuscript for submission to Springer Intensive Care Medicine under the title "Physical function and related factors in critical illness survivors: A Scoping review". (ADDENDUM A**)**

2.1 Introduction / Background

As the survival rates of critically ill patients have grown,(30) so has our interest in the outcomes of survivors and understanding the patterns of recovery.(31) Outcomes of interest have grown from the short term, merely expressing mortality, to long-term morbidity.(5)

A large focus of research has been to identify impairments, across the course of critical care, that contribute to the consequences of critical illness.(1) Survivors experience long term complications in physical function, psychiatric function and HRQoL.(4) A new term to describe these worsening impairments in function (physical, mental and cognitive) is PICS.(1) These impairments develop during critical illness and persist after hospital discharge.(1)

PICS has been identified as one of the largest health challenges in survivors of critical illness.(22) This review took a particular interest in physical function as a major contributing factor to PICS. Substantial impairments in physical function outcomes have been demonstrated years after discharge.(14) Physical function has also been associated with various other outcomes, within PICS, such as decreased HRQoL and mental health impairments (increased anxiety).(32) Importantly outcomes of physical function and muscle weakness are related to LOS, post discharge survival and return home.(5)

In addition, physical function has been identified as one of the core outcomes for assessment in the critically ill population.(3,22,33) There is however still a lot of uncertainty as to how and when physical function should be measured in this population. Frequently used measures survey an array of different limitations in activities of daily living (ADL's) and exercise tolerance.(1,4,34) Another consideration

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in the assessment of physical function is the difference between patient self-reported outcome measures and performance-based outcome measures, which may inform different facets of physical function that are not always correlated.(7) In an international modified Delphi consensus study, to determine core outcome measurement tools, no outcome measures reached consensus for the evaluation of physical function.(3,33) Demonstrating the complexities of measuring physical function outcomes and determining its assessment within this patient population.

To provide context for the current literature we thus decided to conduct a scoping review utilising the impairment domains of PICS (1) and the constructs of the ICF framework, developed by the WHO,(2) to determine how physical function is investigated in the literature. The ICF helped to describe the intricate and multi-dimensional concept of function,(35) across three distinct constructs: body structure and function, activity limitations and participation restrictions. Our work builds on other studies that have also utilised the ICF framework to investigate both physical function (5,7) and PICS (7) in the literature.

The aim of this review was therefore to map the existing literature describing physical function in critical illness survivors within the three constructs of the ICF; how and when it has been reported; as well as describe impairments in mental health as it relates to physical function within PICS. We propose that by unpacking the physical function outcomes reported in ICU survivors the results from this review could assist in the development of a research agenda.

2.2 Methods

A scoping review was conducted and guided by the five-stage framework published by Arksey and O'Malley,(17) to map current research activity in the field of physical function outcomes in critically ill patients. This scoping review was also reported in accordance to the guidelines for scoping reviews, as set out in the PRISMA_Scr guidelines.(37)

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Framework stages are as follows:

Stage 1 - Identifying the research question

Stage 2 - Identifying relevant studies

Stage 3 - Study selection

Stage 4 - Charting the data

Stage 5 - Collating, summarising and reporting the results

2.2.1 Stage 1 Identifying the research question

We report on physical function from two vantage points. The first vantage point was from the concept of PICS which is described as new or worsening impairments in physical, mental or cognitive function that develop during critical illness and persist after hospital discharge.(1) Numerous factors have been described under the physical impairment domain of PICS.(1,34) We report on physical function as a major contributing factor to the physical impairment domain described in PICS (Figure *2.1*).(1) We decided to include the impairment domain of mental health in ICU survivors as they relate to physical function (Figure *2.1*). In an attempt to identify coexisting impairments in mental health and physical function within PICS.(34)

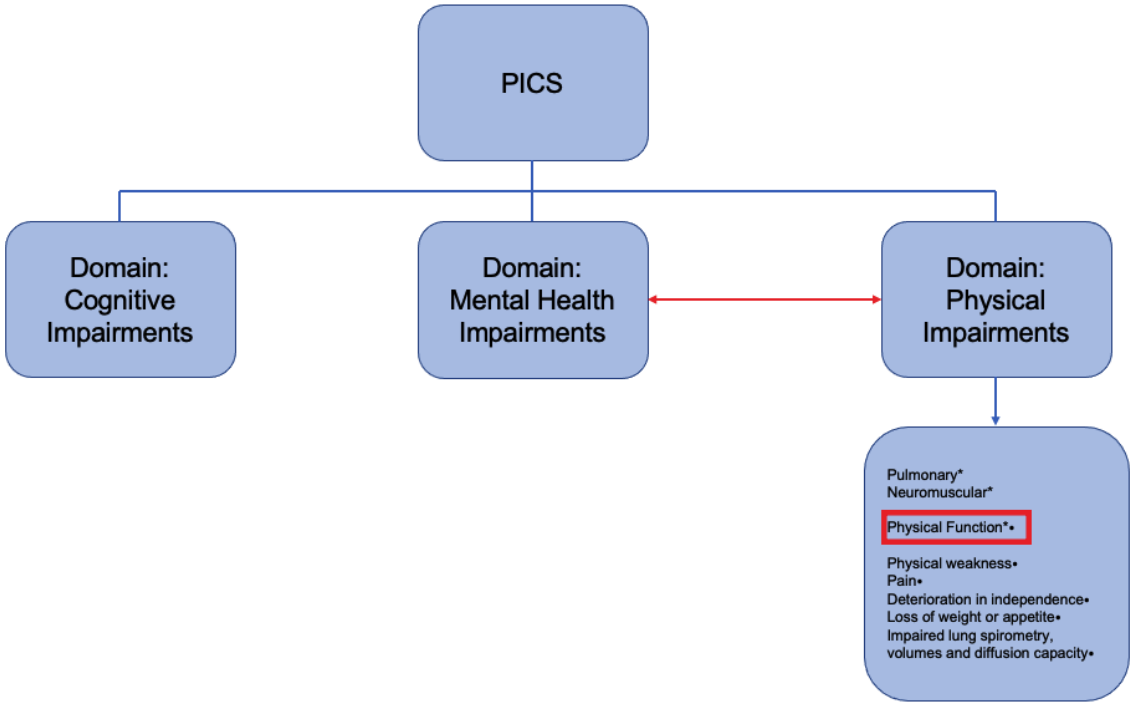

Figure 2.1: **Representation of physical function as a major contributing factor to Post Intensive Care Syndrome (PICS)**
**=factors in physical impairments identified by Needham et al.* (1) *•= factors in physical impairments identified by Yuan et al.* (34)

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The second vantage point was reporting on physical function under the ICF framework (Figure *2.2*). Physical function was reported as the measurement (self-reported or performance-based) of limitations in specific activities (e.g., walking) or ADL's within the ICF constructs of activity and participation. We then aimed to identify possible contributing factors in "body structure and function" that might cause these limitations. We focused on body structure and function (physiologic) factors of the neuromusculoskeletal and cardiopulmonary body systems.(1,5)

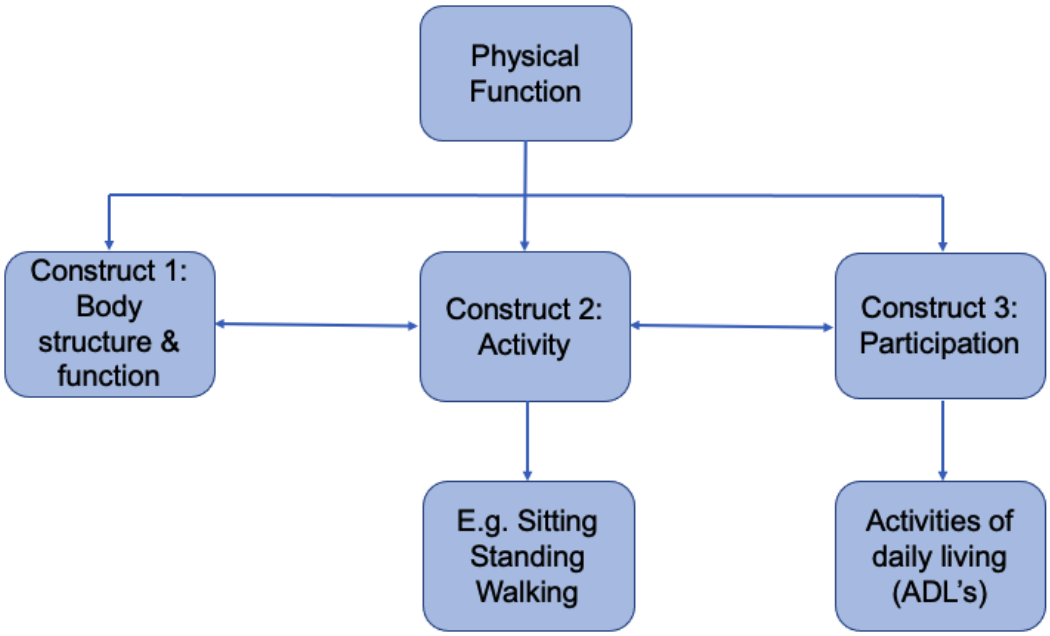

Figure 2.2: **Physical function reported on according to the International Classification of Function (ICF) framework**

We thus included the following constructs as it relates to physical function:

Construct 1: Activity: We described the measures of specific activities used to assess physical function including but not limited to the six-minute walk test (6MWT).

Construct 2: Participation: We described the measures of ADL's used to assess physical function including but not limited to the instrumental acts of daily living (IADL).

Construct 3: Body structure & function: We described factors of neuromusculoskeletal and cardiopulmonary body systems.

In conclusion, we describe mental health impairments, neuromusculoskeletal- and cardiopulmonary- body systems as factors of interest which have been investigated as it related to physical function of ICU survivors.

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Current research question: How is physical function being investigated in the critically ill population and do mental health impairments, neuromusculoskeletal- and cardiopulmonary body systems contribute to these outcomes?

2.2.2 Stage 2 Identifying relevant studies

2.2.2.1 The objectives of this review were to describe:

- the ICU survivor populations in which physical function has been investigated;
- the outcome measures used to assess physical function and the time frames reported (Construct 1 and 2);
- factors identified in Construct 3 related to physical function in ICU survivors;
- the outcome measures used to assess these factors;
- coexisting factors of mental health, identified in the impairment domain of PICS, as it relates to physical function in ICU survivors;
- the outcome measures used to assess factors in this impairment domain.

2.2.2.2 Search strategy

Six computerised bibliographic databases were searched by the primary investigator (PI), namely PubMed, Scopus, CINAHL, MEDLINE, Science Direct, and Web of Science from inception to September 2019. Search terms were applied with limits on articles in English. Database specific search strategies were developed (ADDENDUM B). The search strategies for each database were verified by a librarian from the Department of Medicine and Health Sciences at Stellenbosch University.

2.2.3 Stage 3 Study Selection

Developing the inclusion and exclusion criteria was an iterative process undertaken by the reviewers while interacting with the literature. Papers were included if they recruited adult (18 years and older), human, critically ill survivors and reported on a physical function measure (self-reported or performance-based) and at least one of the factors of interest described previously (Section 2.2.1). We excluded papers that enrolled neonates, paediatrics, and adolescents, as well as papers performed on animals or those that were not available in English. Research protocols, reviews, intervention studies, studies evaluating the clinimetric properties of outcome measures and studies that exclusively reported on neurologic patients, were also excluded.

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Physical function was defined as a self-report or performance-based outcome measure using the description from each of the included papers methodology or results sections.

The PI and a secondary reviewer (SC) independently and systematically screened and evaluated all publications returned by the search strategy for relevance to the review, at title, abstract and full-text level. In the event of disparities on inclusion, a discussion to reach consensus was arranged between the two reviewers. If consensus was not reached within that meeting, a third reviewer (ALS) was consulted. Full-text papers were retrieved by accessing electronic journals. Search terms as well as a summary of the findings can be found in table form in ADDENDUM B.

2.2.4 Stage 4 Charting the data

The PI extracted and charted relevant data from the included papers in a customised Excel data capture sheet. The data included: the country of origin; year of publication; research design; study setting; study participant pathologies; mean or median age of study population; study assessment period; factors of interest identified (mental health, neuromusculoskeletal or cardiopulmonary); physical function outcome measures used and assessment period; outcome measures used to assess the different factors of interest. The results section of the included papers were used to describe statistically significant associations between factors of interest and physical function.

2.3 Stage 5 Collating, summarising and reporting the results

The total number of search hits from the selected databases included 1 074 papers. Duplicate papers were eliminated, and 315 papers remained (ADDENDUM C). Following the selection process (Figure *2.3*), 13 papers were included in this review.

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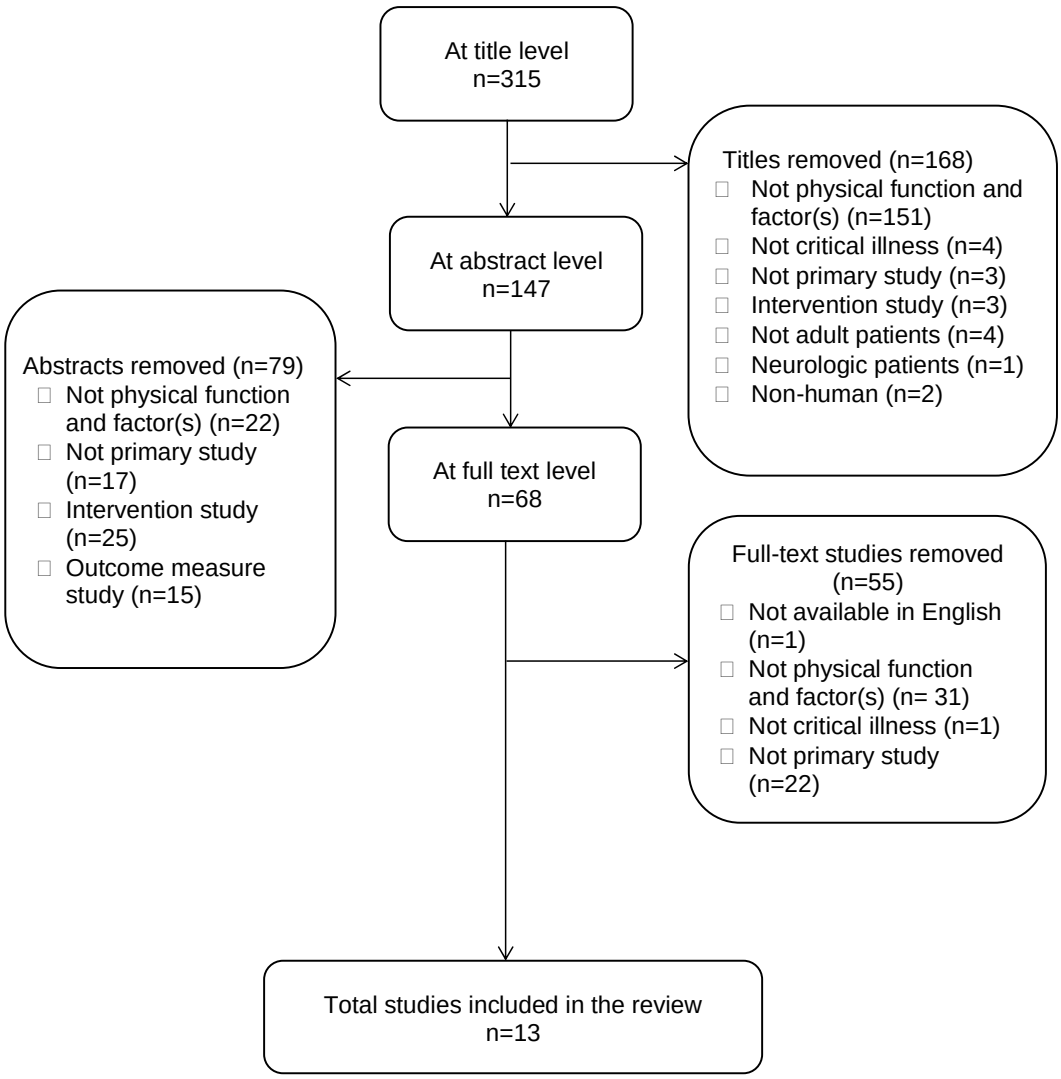

***Figure 2.3*: Selection process flow diagram**

2.3.1 Description of included papers

All studies were conducted in developed countries from three continents. The majority of studies (n=7 [54%]) were conducted in North America with five published in the United States of America (38–42) and two in Canada.(31,43) Three studies emerged from Europe; Greece (n=1) [8%],(44) Germany (n=1 [8%]) (45) and Denmark (n=1 [8%]).(46) Three studies emerged from Australia.(47–49) No studies were identified from Africa, Asia, or South America. Most of the studies conducted were prospective longitudinal cohort studies (n=12 [92%]).(31,38–47,49) One other study was a cohort analysis (n=1 [8%]).(48)

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2.3.2 Year of publication

Figure *2.4* shows the number of studies published per year. The first papers describing physical function linked to a factor of interest were published in 2011. Three papers were published in 2019.

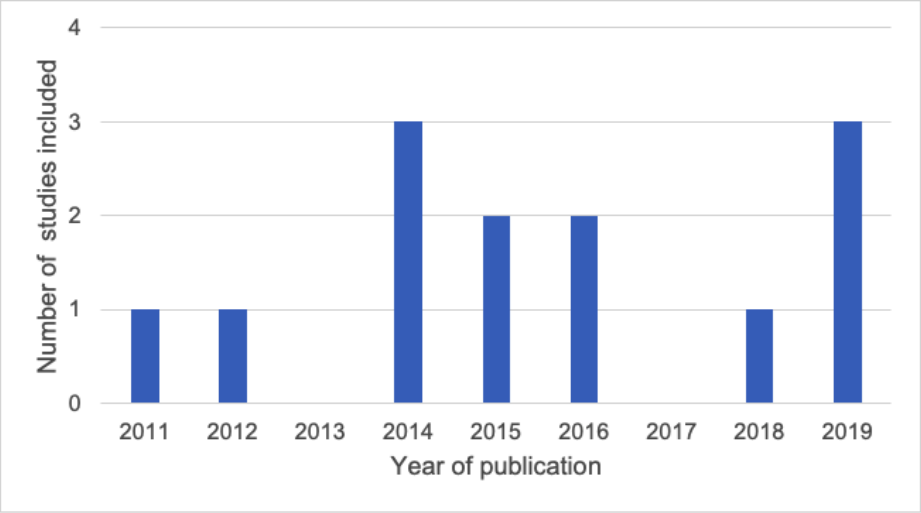

***Figure 2.4*: Number of studies published per year**

2.3.3 Population

The demographics of the populations included in this review are summarised in Table 2.1. The majority of studies included data from mixed units (n=7 [54%]) and a variety of primary diagnosis. The majority of studies (n=11 [85%]) included data from male dominant cohorts and participants aged between 40 and 60 years (n=11 [85%]).

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Table 2.1: Included papers study settings and baseline characteristics.

Authors	Type of ICU				Pathologies/ Diagnosis Types								Age (Mean SD/ Median IQR)	% Male
	Medical & Surgical	Surgical	Trauma	NR	ARDS	ALI	Respi-ratory	Sepsis	Cardio-vascular	Trauma	Other	NR		
Hayes et al. (47)	√				√						√		49.3 (SD14.4)	44
Bienvenu et al. (38)	√					√							49 (SD14)	56
Bienvenu et al. (39)	√					√							49 (SD14)	56
Hamilton et al. (43)	√						√	√		√	√		56 (IQR 45-65)	58
Herridge et al. (31)	√				√								45 (IQR36-56)	55
Sidiras et al. (44)	√						√	√	√	√	√		ICUAW 58 (SD13) No ICUAW 51 (SD16)	65
Koch et al. (45)		√			√					√	√		46 (NR)	77
Fan et al. (40)				√		√							52 (IQR 42-63)	56
Pfoh et al. (41)				√	√	√							49 (IQR 41-58)	55
Estrup et al. (46)				√								√	72 (SD10)	59
Aitken et al. (49)			√							√			37 (IQR 28-55)	83
Aitken et al. (48)	√						√		√		√		57 (NR)	70
Needham et al. (42)				√		√							48 (15)	49

√=Yes, ICU= Intensive Care Unit; NR=Not reported; ARDS=Adult Respiratory Distress Syndrome; ALI=Acute Lung Injury.

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2.3.4 Vantage point one

2.3.4.1 Physical function reported in relation to Construct 1 of the ICF

Five of the included studies reported on physical function within Construct 1 of the ICF, activity limitation. Various specific activities were assessed using a number of different outcome measures. Three of the included studies evaluated walking using the six-minute walk test (6MWT). (40,42,48) Two of these studies evaluated physical function by means of the 6MWT at each of the following time points: on or before 6 months (40,48), on or before 12 months (40,42) and between one to three years.(40,42) One study assessed various mobility specific activities using the ICU mobility scale (IMS).(47) These activities include sitting, standing, walking and transferring to a chair. Hayes et al. (47) performed their assessments on day 1 and day 20 in hospital but did not report whether these time frames were during ICU or ward stay. The last study used the Chelsea Physical Assessment tool (CPAx) to assess various specific activities.(46) These activities include coughing, respiratory function, grip strength, moving in the bed, transferring to a chair, sitting, sit to stand and stepping. The CPAx outcome measure was used at ICU discharge and three months. All three different outcome measures used to assess activity limitations were performance-based assessment measures.

2.3.4.2 Physical function reported in relation to Construct 2 of the ICF

A number of studies (n=8 [62%]) reported on physical function within Construct 2 of the ICF, participation restriction.(31,38,39,43–45,49) Four different outcome measures, Instrumental activities of daily living (IADL);(38,39) functional independence measure (FIM);(43,44) 36 item short form survey physical component score (SF 36 PCS);(31,38,41,49) and functional health status questionnaire (FHSQ),(45) were used to assess ADL's. These were all self-report outcome measures. Even though these outcome measures were described as self-report measures, the IADL was completed by either participants or their proxies.(38,39)

Physical function assessments using outcome measures of ADL's were performed at hospital discharge (44), on or before 6 months,(31,38,39,43–45,49) on or before 12 months (31,38,39,43–45,49), between 1 to 3 years (31,38,39,41,43,45,49) and between 3 to 5 years.(31,41)

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2.3.4.3 Physical function reported on, within the impairment domains of PICS, in relation to factors of mental health

The mental health impairment domain of PICS, as it relates to physical function, was most frequently assessed by measures of anxiety,(38,49) depression (38,39,43,48) and post-traumatic stress disorder (PTSD).(38,48,49) Two studies evaluated all the factors as stated (38,48), two evaluated depression only (39,43) and one study evaluated PTSD symptoms along with various other mental health impairments.(49)

Anxiety and depression were assessed by means of two different measures. Two studies used the hospital anxiety and depression scale (HADS) (38,39) and another study used the anxiety and depression stress scale (48), to assess the same symptoms. Depression was assessed using the Beck depression inventory (BDI-II).(43)

PTSD symptoms were also assessed using two different measures. Namely the impact of event scale reviewed (IESR) (38,48) and the PTSD checklist civilian version.(49) The other mental health impairments were assessed as follows: psychological distress by means of Kessler Psychological Distress Scale, illness perception by means of Brief Illness Perception Questionnaire, self-efficacy by means of the self-efficacy scale (SES) 36 and perceived social support by means of Multidimensional Scale of Social Support.(49)

2.3.5 Vantage point 2

2.3.5.1 Physical function reported in relation to factors of the neuromusculoskeletal body system (Construct 3)

Six studies reported on factors of the neuromusculoskeletal body system as it relates to physical function.(40–42,44,45,47) Muscle strength,(40–42,44,47) muscle structure,(47) myopathy and polyneuropathy (45) were used as measures of the neuromusculoskeletal body system which could affect physical function.

All the studies evaluating peripheral muscle strength used the medical research council sum score (MRC-SS) a manual muscle test.(40–42,44,45,47) One study used a second measure handheld dynamometry (HHD), to assess peripheral muscle strength.(47) Grip strength was measured with HHD (40,42,44) and maximal

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inspiratory pressure (MIP) was used to assess respiratory muscle strength.(40,42) Ultrasonography (US) (47) was used to assess muscle structure and electrophysiological testing to identify both critical illness myopathy (CIM) and polyneuropathy (CIP).(45)

2.3.5.2 Physical function reported in relation to factors of the cardiopulmonary body system (Construct 3)

The cardiopulmonary body system was assessed using measures for exercise tolerance,(31,41) activity levels,(46) pulmonary function and pulmonary structure.(31) Two studies used the 6MWT as an assessment measure for exercise tolerance.(31,41) Herridge et al. (31) investigated pulmonary structure through computed tomography (CT), and pulmonary function by means of spirometry. Activity levels were evaluated using actigraphy.(46)

2.3.6 Factors of interest associated with physical function outcomes

Three of the studies assessing physical function within Construct 1 of the ICF, as limitations in specific activities, evaluated factors of the neuromusculoskeletal body system.(40,42,47) The specific activities assessed was walking using the 6MWT (40,42) and other mobility specific activities using the IMS.(47) (See Table 2.2)

Two of these studies assessed muscle strength as a factor of the neuromusculoskeletal body system. A reduction in peripheral muscle strength or identifying ICU-AW by peripheral muscle testing was shown to have statistically significant associations with outcomes in physical function within Construct 1.(40,42) Assessments of grip and respiratory muscle strength were also associated with physical function outcomes in this construct.(42)

Physical function assessed within Construct 2 was most frequently assessed along with factors of the mental health impairment domain. Four of the included studies that evaluated participation using measures of ADL's also assessed factors of mental health.(38,39,43,49) (see Table 2.2) The mental health factor of depression demonstrated statistically significant associations with physical function in two of these studies.(38,43) Physical function was assessed using the SF-36 PCS in two of these studies.(38,49)

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Table 2.2: **Factors of interest investigated in relation to physical function.**

Author	Cardiopulmonary-vascular				Neuromusculoskeletal				Mental Health				Physical Function						
													Activity			Participation			
	Exercise tolerance	Activity Levels	Pulmonary Structure	Pulmonary Function	Muscle strength	Muscle structure	Myopathy	Poly-neuropathy	Depres-sion	Anxiety	PTSD	Other	IMS	6MWT	CPAx	IADL	FIM	FHSQ	SF-36 PCS
Hayes et al. (47)					√	√**							√						
Bienvenu et al. (38)									√	√**	√**					√			√
Bienvenu et al. (39)									√**							√			
Hamilton et al. (43)									√**								√		
Herridge et al. (31)	√**		√	√															√
Sidiras et al. (44)					√**												√		
Koch et al. (45)					√		√	√**										√	
Fan et al. (40)					√**									√					
Pfoh et al. (41)	√				√														√
Estrup et al. (46)		√**													√				
Aitken et al. (49)											√	√**							√
Aitken et al. (48)									√**	√**	√			√					
Needham et al. (42)					√**									√					

*√=Yes, ** Represents significant associations with physical function. Other mental health impairments= psychological distress, illness perception, self-efficacy and perceived social support. PTSD= Post Traumatic Stress Disorder; IMS=ICU mobility scale; 6MWT=six-minute walk test; CPAX= Chelsea critical care physical assessment tool; IADL=Instrumental acts of daily living; FIM= Functional Independence Measure; FHSQ= Functional Health Status Questionnaire; SF36 PCS= SF36 physical component score.*

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A summary of the identified factors of interest, in critical illness survivors, relating to physical function are represented in Figure *2.5*.

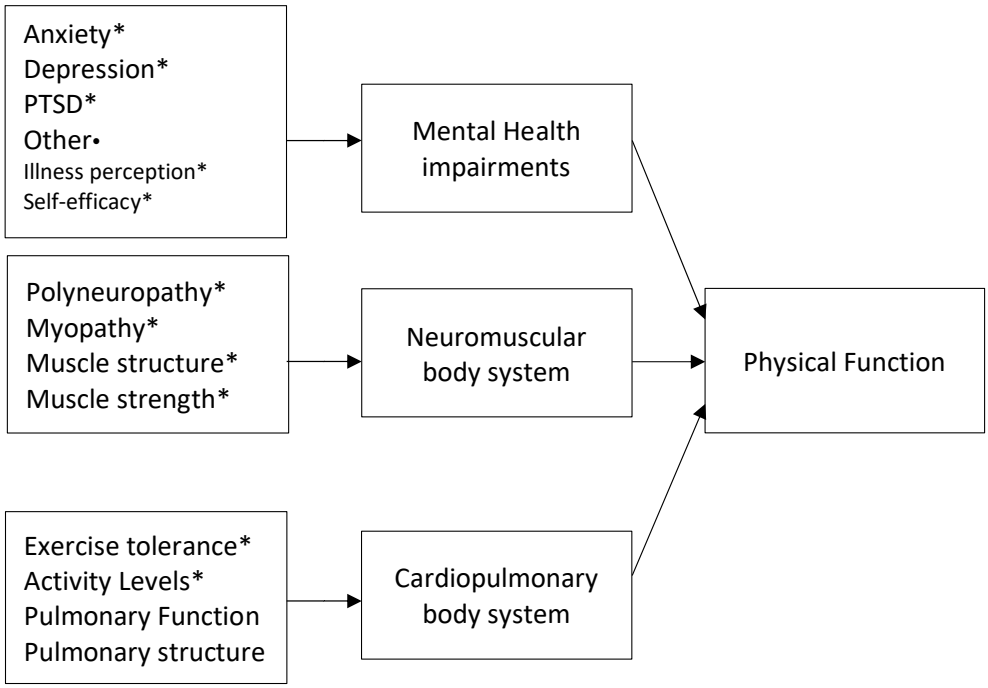

Figure 2.5: **A representation of the identified factors of interest related to physical function outcomes**
• Other= psychological distress, illness perception, self-efficacy and perceived social support.
** = significant associations with physical function. Muscle strength= peripheral, respiratory and grip strength*

2.4 Discussion

Our review highlights the fact that underlying factors potentially related to poor physical function have not been fully explored to date. While physical function outcomes of ICU survivors have been investigated since the late 1900's (7) and were incorporated into the concept of PICS in 2012,(1) this review indicates that more focused work is needed in this field. Physical function is a complex concept which can explain the variety of factors investigated in relation to physical function outcomes in the literature. However, it is concerning that studies included in this review took a one-dimensional approach in the evaluation of physical function.

None of the included studies in this review investigated physical function as both activity limitations and restrictions in participation (ICF Construct 1 and 2) whilst still investigating possible factors associated with these outcomes. Even though

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considerations for evaluating physical function have been described, within both these constructs of the ICF, specifically within critical care.(5)

There were however studies that included measures of specific activities, the 6MWT, and a measure of physical function but within the description of these studies the 6MWT was used in the assessment of exercise tolerance.(31,41) There was no clear link made between this specific activity assessment and the assessment of physical function. In these studies, physical function was assessed using a different measure, as described in the methods or results sections, and thus for the purposes of this review only described physical function as a measure of participation restrictions.

Other studies again described physical function assessment as the limitations in the specific activity of walking using the 6MWT,(40,42,48) but did not assess physical function as limitations in ADL's within the construct of participation restrictions. Highlighting the fact that the link between assessing physical function as both activity limitation and participation restriction, is not being made.

It is thus clear that there is still a need to determine consensus on how to assess physical function in the critically ill population, and which outcome measures to use. Many outcome measurement tools have been considered in the evaluation of physical function in this population, but none have reached consensus.(3) The use of standardised and validated outcome measures to assess physical function are imperative to allow for synthesis of results across studies.(3)

To address this problem, we suggest conducting physical function assessments through a combined approach. Using both a measure of activity and participation. Most likely in the form of a self-report and performance-based measure, for example the 6MWT and FIM. This would incorporate the assessment of more aspects of this complex outcome. This is beneficial as it would reveal physiological outcomes and patient-perceived outcomes of physical function.(7)

It is evident from this review that physical function is being evaluated for time frames long after discharge. However, research evaluating physical function and any of the various factors of interest for time frames both in-hospital and after discharge, are

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lacking. In-hospital evaluation of physical function is paramount to inform clinical decision making, and to assist in early identification of those at risk of poor outcomes. Identifying those at risk could inform in-hospital intervention and post-discharge rehabilitation strategies. Post-discharge assessments are needed to inform long term outcomes and describe the course of recovery from critical illness and PICS.

2.4.1 Limitations

The development of the inclusion and exclusion criteria for this review was an iterative process but articles were limited to the English language. There is a possibility that eligible studies may have been unknowingly excluded if they were only available in the language of origin, as this review only included research articles already published in English, without the need for translation.

This review only reported on the impairment domain of mental health. The impairment domain of cognitive function within PICS, as it related to physical function, was not reported. Future research is needed to investigate possible associations between the outcomes of physical function and cognitive impairments.

2.4.2 Implications for future research

Research on physical function and the factors of interest is needed in developing countries, where no such research was identified within this review. More research is required to evaluate numerous factors of interest and their relation to physical function, to try and better determine possible associations.

Factors that were not as frequently evaluated and described in association to physical function include: respiratory muscle strength, grip strength, muscle structure, pulmonary structure and function, and the other mental health impairments.(49)

Even though we see that physical function is being evaluated, future research is needed to investigate this complex outcome as both activity limitations and restrictions in participation. Time frames for assessment of physical function should include assessments both in hospital and post discharge, to allow for better evaluation of outcomes and the consequences of critical illness.

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From the included literature the proposed research agenda is:

- determining a baseline on physical function outcomes, within Construct 1 and 2, of critically ill patients in a developing country (SA);
- assessing physical function, along with factors of interest, which have been shown to have associations with outcomes in physical function (peripheral and respiratory muscle strength), to describe their possible relation to physical function outcomes;
- assessing physical function along with factors of interest that require further investigation: muscle structure.

2.4.3 Conclusion

Physical function is being evaluated as an outcome of interest in the critically ill population, but the number of articles reporting on both physical function and possible relating factors are limited. Physical function is a complex outcome with multiple factors impacting these outcomes. A one-dimensional approach to assessing physical function is being taken within the current literature. Therefore, further investigation is required to assess physical function as both limitations in activity and restrictions in participation, and relating factors such as peripheral and respiratory muscle strength, pulmonary structure and function, and muscle structure.

Conflict of interest

None.

Funding sources

None.

Ethical approval form

This article is a scoping review and therefore ethical approval was not required.

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CHAPTER 3 : METHODOLOGY OF PRIMARY STUDY

We developed a primary study informed by the results of the scoping review. The primary study was developed to answer the following question: What are the outcomes in physical function, muscle function, and HRQoL of patients admitted to a privately funded hospital ICU in SA?

This chapter explains the research process used to answer the research question. It provides information concerning the methods that were used to undertake this research, as well as the justification for the use of these methods and materials. This chapter also describes the timeline at which each outcome was assessed during the research process, the selection of participants, the process of data collection and data analysis.

3.1 Project Aim

To describe the baseline demographic characteristics and critical illness factors, physical function, muscle function, and HRQoL outcomes, up to three months post discharge, of patients admitted to a privately funded hospital ICU in SA.

3.2 Project Objectives

3.2.1 Primary Objectives:

- To describe the demographic characteristics and critical illness factors of patients admitted to private hospital ICU
- To describe the change in muscle structure and function, of peripheral and respiratory muscles, from ICU admission up to hospital discharge
- To describe the exercise tolerance of patients at hospital discharge
- To describe physical function using both “performance-based” (to assess limitations in specific activities) and “self-reported” (to assess restrictions in participation) measures at hospital discharge
- To describe “self-reported” physical function at three months after discharge
- To describe the health-related quality of life (HRQoL) of patients at hospital discharge and three months after hospital discharge

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3.2.2 Secondary objectives:

- To describe the return to work of patients at three months after hospital discharge
- To describe the healthcare utilisation and mortality at three months after hospital discharge of patients admitted to a private ICU

3.3 Study Design

A prospective observational cohort study. This study forms part of a larger project: “The impact of critical illness on muscle structure, strength and physical capability” (Ethics Approval Number: S16/09/173A) (ADDENDUM D).

3.4 Research Setting

This study was conducted in a private hospital in the Western Cape Province of SA. This institution has three respective intensive care units: 1) Critical care unit, 2) Cardiology critical care unit, and 3) Cardiothoracic critical care unit. Two of the three units are run as closed units managed by the respective anaesthetist’s and the third unit is an open unit.

The individual critical care units have 12 beds (Cardiology critical care unit and Cardiothoracic critical care unit) and 9 beds (Critical care unit) respectively. In total there were 33 critical care beds within this hospital.

3.5 Ethical considerations

HREC approval (S18/08/176) (ADDENDUM E) was granted prior to data collection. Permission to conduct the research study was obtained from this private hospital prior to data collection (ADDENDUM F). All participants, or participants next of kin, provided written informed consent (ADDENDUM G).

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3.6 Sample

We recruited adult patients over the age of 18, admitted to any of the aforementioned ICU's between 1 February 2019 and 31 July 2019, who were expected to be on invasive mechanical ventilation for >48 hours. Participants were included within the first 24 hours of mechanical ventilation. Participants were excluded if they had new or known neuromuscular disease, spinal cord injuries or intracranial processes. Participants were followed up at three months after hospital discharge, this data was collected until 31 October 2019.

3.7 Routine management of ICU patients in this institution

In bed mobility was initiated by the nursing staff. Patients were turned two hourly and pressure care performed unless contra-indicated. Glucose control protocols were in place with both intravenous and intramuscular treatment options. Different protocols also exist for patients with diabetes mellitus (DM) and patients with other critical illnesses requiring glucose control. The specific sedation used was determined at the discretion of the anaesthetist's or specialist in charge of the patients' care. The sedation was documented as part of the medication on the bed charts and sedation level was documented in each of the critical care units by means of the Richmond Agitation and Sedation Scale (RASS). This was documented on the ICU bedside chart. Weaning from invasive mechanical ventilation in this setting was determined by the anaesthetist's or specialist in charge of the patients care on an individual basis. Patients' ventilatory modes and means were re-viewed daily and adapted as deemed appropriate by the anaesthetist or specialist in charge.

Physiotherapy management was performed by one of three practices that consult within this private institution. Group A manages mostly adult neurologic conditions and consulted patients once a day unless otherwise indicated or prescribed by the anaesthetist. Group B manages mostly cardiology and cardiothoracic admissions and treatments occurred mostly twice daily. Group C manages orthopaedic, post-surgical and medical admissions and their treatment took place once a day unless otherwise prescribed or indicated. All physiotherapy groups administered respiratory and

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mobility interventions as part of their treatment. In the critical care units, early mobility-based management was performed unless contra-indicated or specified by the managing anaesthetist or specialist in charge.

3.8 Demographic characteristics and critical illness factors:

Data on demographic characteristics and critical illness factors were collected from the participant's file by the PI. This included: age, gender, height, weight medical co-morbidities, admission diagnosis and Simplified Acute Physiology Score 3 (SAPS 3), date of intubation and employment status.

SAPS 3 was calculated and documented electronically as part of standard practice in this private hospital. This score is used as an indication of severity of illness within the ICU setting as it can predict ICU mortality.(50) Theoretically this score can range from 0 to 217, with a higher score being indicative of more severe illness.(51) The SAPS 3 has been found to perform similarly to the APACHE II and SAPS II.(54) The variables to calculate the SAPS 3 score were entered into an online platform by the ward administrator.

The following exposure variables were selected a priori and reported for the first three days of ICU admission: Ventilation mode, blood results (WCC, CRP, HGT, blood pH) if available, average of the patients Richmond Agitation and Sedation Scale (RASS) for each day, and medication exposures to corticosteroids, sedation agents and neuromuscular blocking agents (NMBA's).

The RASS score is used as part of standard practice in this facility and this score is documented on the patient's ICU bedside chart. It is used to determine level of sedation or consciousness within the ICU setting. The RASS score is a 10-point scale with levels for anxiety or agitation (+1 to +4[combative]), alert or calm state (0) and levels of sedation (-1 to -5) ending in unarousable (-5).(52) The RASS has also been proven to have validity for use in the adult intensive care unit.(53)

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Length of ventilation (LOV) and LOS in ICU was calculated, in days, by the PI from the data as recorded in the bedside chart at ICU discharge. The LOV was calculated from the time of intubation to the time of extubation by the PI. LOS in ICU was calculated from the day of ICU admission to the day of ICU discharge. On the day of hospital discharge, the total LOS was calculated, discharge destination, and mortality were reported. Total LOS in hospital was defined as the total amount of days spent in hospital from ICU admission to discharge.

3.9 Description of selected outcomes

The outcomes selected for measurement in this research study were identified in 1) the scoping review (Chapter 2), as factors of the neuromusculoskeletal- and cardiopulmonary body systems relating to physical function outcomes in the critically ill population, and 2) as part of the core domains in evaluating patient outcomes for ICU survivors.(3,22,23)

These outcomes were categorised by: 1) the ICF as set out by the WHO (2) and 2) the core domains in evaluating patient outcomes of ICU survivors. (22) An attempt was made to look at all the constructs of function (body structure and function, activity limitation and participation restriction), within the ICF,(2) while still including minimum important domains set out in the COMS.(3) We attempted as far as possible to use the outcome measures for these domains that reached consensus in the COMS.(3) (See Table 3.1)

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Table 3.1*:* ICF classification and COMS domain, outcomes selected, and outcome measures used.

ICF construct	COMS Domain	Outcome Observed	Outcome measure used
Body structure and function	Muscle function	Muscle structure	US peripheral & respiratory muscles
		Muscle strength Peripheral & Respiratory	MIP
			MRC-SS& HHD
		Muscle endurance	Respiratory muscle endurance
Activity limitation	Physical function	Physical function performance-based measurement	CPAx
		Exercise tolerance	6MWT
Participation restriction	Physical function	Physical function self-report measurement	BI
	HRQoL & pain	HRQoL	EQ-5D

ICF= International Classification of Function; COMS=core outcome measurement set; US= ultrasound; MIP= maximal inspiratory pressure; MRC-SS= Medical Research Council Sum Score; HHD= handheld dynamometry; CPAX= Chelsea critical care physical assessment tool; 6MWT= six-minute walk test; BI= Barthel Index; HRQoL= health related quality of life; EQ-5D= EuroQol five dimensions.

3.10 Data collection procedure

As described in Section 3.8 baseline data were collected from patient bedside chart and medical files by the PI. Outcome measurements as described in Table 3.1 were recorded using a standardised data capture sheet (ADDENDUM H). All assessments using the various outcome measures at each time point were obtained by the PI (See Figure *3.1*)

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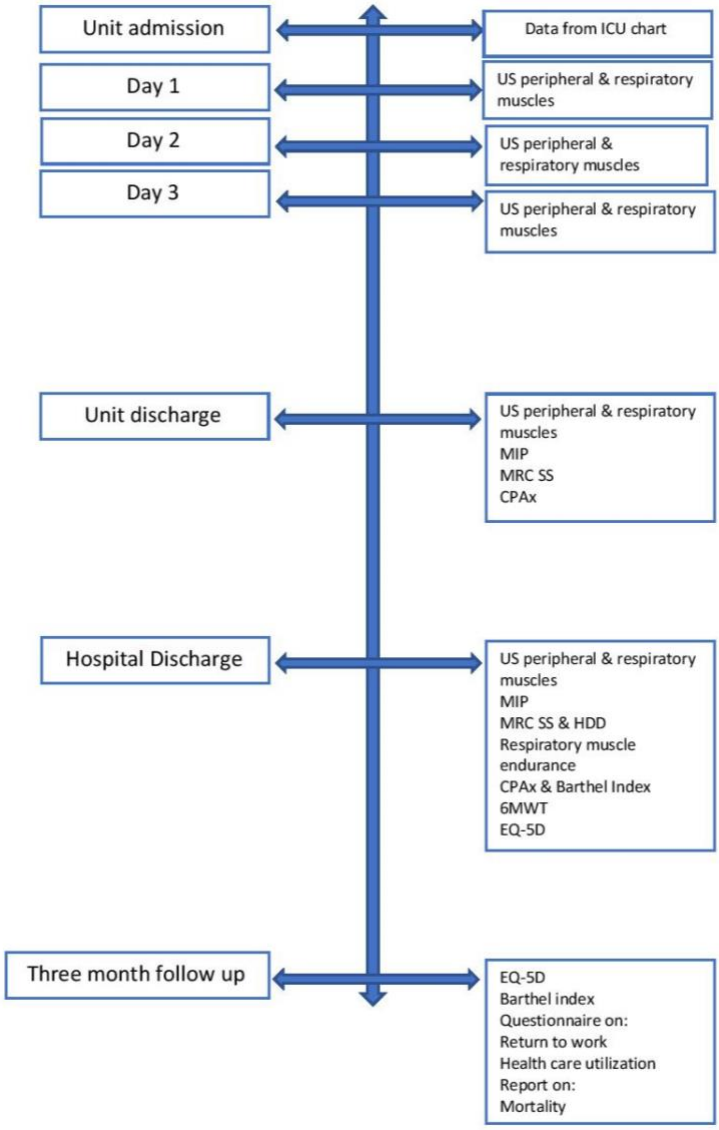

Figure 3.1: **Timeline of outcome measures**
ICU= intensive care unit; US= ultrasound; MIP= maximal inspiratory pressure; MRC-SS= medical research council sum score; CPAx= Chelsea critical care physical assessment tool; HHD= hand-held dynamometry; 6MWT= six-minute walk test; EQ-5D= EuroQol five dimensions.

3.11 Description of selected outcome measures

3.11.1 Muscle structure and function

3.11.1.1 Peripheral and respiratory muscle structure via ultrasound (US):

The Rectus Femoris (RF) and Vastus Intermedius (VI) muscles were assessed in supine with the participants knee in passive extension and neutral rotation. The point of reference, where the transducer was placed, was perpendicular to the long axis of the thigh on its anterior surface, two thirds of the distance from the anterior superior

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iliac spine (ASIS) to the superior patellar border.(54) Three pictures were taken and the average of the three measurements used to determine muscle thickness. Muscle thickness was recorded in centimetres (cm). The images taken were grey scaled and the gain set and standardized. Three images were analysed at each of the time points, and the mean pixel intensity was calculated to determine echogenicity.(15,54)

The RF and VI muscle thickness were investigated as a method of detecting muscle atrophy and echogenicity as an indication of muscle quality.(15) These muscles were chosen specifically as the RF muscle has been shown to demonstrate larger changes in muscle thickness and VI in echogenicity.(15)

Muscle structure was assessed for the first three days in ICU, at ICU and hospital discharge. The Samsung Medison MySonoU6 (Samsung Company, Seoul, Korea) with a high frequency linear array transducer was used for the collection of data with US. Images were analysed offline using Image J software (NHI, USA).

Assessments of diaphragm thickness (tdi) were performed on the right-hand side in the zone of apposition as has been previously described.(58) Images of the diaphragm were recorded in loops of three full tidal breathing cycles (from inspiration to expiration). These loops were stored and the average thickness, for inspiration and expiration, during each of the three breaths were included in the data set along with a calculation for diaphragmatic thickening fraction (DTF).

Measures of diaphragm thickness were included in this dataset to investigate diaphragmatic atrophy. Multiple studies have suggested that patients on mechanical ventilation experience diaphragmatic atrophy and dysfunction.(16,20,56)

DTF has been shown to be indicative of weaning success (57–59) and it may be an indication of diaphragmatic function and respiratory workload.(60) DTF was calculated as follows:(57,58)

$$\frac{\text{(thickness at end inspiration – thickness at end expiration)}}{\text{thickness at end expiration}} \times 100 = \%$$

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The intra- and interrater reliability for measures of peripheral and respiratory muscle structure with US was determined through a pilot study (ADDENDUM I).

To describe change in both peripheral and respiratory muscle structure participants were grouped according to their individual percentage change between day one and day two in ICU. The measures of each participant at day two were compared to their own baseline measurement on day one of ICU admission and the percentage change in DTF, peripheral muscle thickness, and echogenicity were calculated. Three groups were established. The cut-off values for these three groups were as follows: a decrease of more than 10% (decrease group), less than 10% increase or decrease (unchanged group) and more than 10% increase in measures (increase group). This grouping method was similar to those previously described.(61)

3.11.1.2 Peripheral muscle strength:

Peripheral muscle strength was assessed using two outcome measures. Both these outcome measure assessments were performed according to previously described guidelines.(64) Manual muscle testing was performed for the upper and lower limbs by means of the MRC-SS. A total score for each participant was calculated out of 60. A score of less than 48 has been shown to be indicative of ICU-AW.(17,63) A second measure of muscle strength was included as the MRC-SS has been shown to have a ceiling effect in identification of less severe muscle weakness.(32)

Handheld dynamometry (HHD) was performed, in combination to the MRC-SS, using the ErgoFET2 dynamometer (Hoggan Health, USA) for the upper limb (during shoulder abduction) and the lower limb (during knee extension). The score was measured in Newtons. The percentage of the predicted normal values was calculated using equations as published by Bohannon (67) for both UL and LL HHD of each participant.

To familiarise patients with the movements when using the HDD, it was first passively performed by the PI and the patient was then asked to perform the movement actively against the dynamometer. Three repeated isometric contractions were performed and recorded. Measures had to be within 10% of one another, if not the measurement was

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technically not satisfactory.(62) The highest of the three measurements were included in the dataset.

Peripheral muscle strength was performed by means of MRC-SS at ICU discharge and by means of both MRC-SS and HHD at hospital discharge.

3.11.1.3 Respiratory muscle strength:

To assess respiratory muscle strength patients were positioned in sitting. MIP was measured by use of a manometer, the POWERbreathe, KH2 (POWERbreathe International Ltd, UK). This was measured through a mouthpiece after a maximal exhalation (at residual volume). These assessments were performed according to the American Thoracic Society (ATS) guidelines on respiratory muscle strength testing.(65) Three measures were carried out and the best of the three were included. Measures needed to be within 10% of each other to ensure that participants' maximal efforts were recorded. MIP was recorded as cmH_20. This was assessed at ICU and hospital discharge.

3.11.1.4 Respiratory muscle endurance:

There is no current measure for respiratory muscle endurance that has been validated within the critically ill population. The proposed method was based on similar evaluation for patients with Chronic Obstructive Pulmonary Disease (COPD) during an inspiratory muscle training protocol.(66) This was tested by asking patients to breathe against a sub maximal inspiratory load provided by a flow resistive loading device, the POWERbreathe KH2, until task failure. The resistive load the device offers during the breathing cycle is determined by a calibrated spring within the device. This load can be calibrated to an individually set load intensity (cmH_2O). The inspiratory load selected was 50% of each participants' MIP. The number of breaths taken, and total respiratory cycle duration was recorded at hospital discharge.

3.11.2 Physical function

Physical function was assessed using two measures, the Chelsea critical care physical assessment tool (CPAx) and Barthel Index (BI).

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3.11.2.1 Performance based physical function using the CPAx:

The CPAx is a 10-item score where a participant can score points from zero to five, ranging from most dependence to most independence, for an individual activity.(67) The 10 activities included in the CPAx are as follows: respiratory function, cough, moving within the bed, supine to sitting on the edge of the bed, dynamic sitting, standing balance, sit to stand, transferring from bed to chair, stepping and grip strength (predicted for age and gender on the dominant hand).(67) A total score out of 50 was calculated once all the activities were evaluated. The CPAx assessment was performed according to the published guidelines.(67) This measure was included as a performance-based measure of assessment in activity limitations of physical function. If any activity was not appropriate due to the participant's medical condition it was not assessed. CPAx assessment was performed at ICU discharge.

3.11.2.2 Self-report physical function using the BI:

The BI is another form of physical function assessment which contains 10 items. This index asks the participant to score each item with the statement that most closely corresponds to their current level of ability. If the participant was unable to complete the BI as a self-report it was completed by a family member familiar with the patient's current abilities. The items that are scored include: bowel continence, bladder continence, toilet use, feeding, transfers, mobility, dressing, stairs and bathing. A total score out of a 100 was calculated, according to the guidelines for scoring the BI,(68) at hospital discharge and telephonically three months after hospital discharge. A higher score indicating more independence and a lower score more dependence with ADL's.

3.11.3 Exercise tolerance

Exercise tolerance was assessed according to the ATS guidelines for the 6MWT.(69) The 6MWT is a self-paced test. Patients were asked to walk as far as possible in a six-minute time frame, within a 30 meter clearly marked corridor, at hospital discharge. The distance walked in this six-minute timeframe was recorded, and the percentage of the predicted normal values were calculated. The reference cohort used was that of healthy North Africans older than 40 years.(70) The six-minute walking distance (6MWD) is a commonly used measure of functional exercise capacity in the critically ill population.

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3.11.4 Health related quality of life (HRQoL)

HRQoL was assessed using the EuroQol Five Dimensions (EQ-5D). Participants were asked to choose a statement for each of the activities that best reflects their status of health on the day. One being the most independent and five being the most dependent. The statements for each activity range as follows: no problem, slight problems, moderate problems, severe problems and unable to perform the activity. Thereafter they completed a 20cm vertical visual analogue scale from 0 to 100 to rate their health. This was performed at hospital discharge and telephonically at three months post hospital discharge. The EQ-5D was performed and the results were presented according to the EuroQol Research Foundation EQ-5D user guide.(71) In this study the EQ-5D results were presented as a health profile and according to the Pareto Classification of Health Change (better, worse, the same or mixed) as described in the EQ-5D-5L user guide.(71)

3.12 Validity of outcome measures used

3.12.1 Muscle structure and function

3.12.1.1 Peripheral and respiratory muscle structure via ultrasound (US):

Muscle thickness using ultrasonography has been validated against other imaging study modalities such as magnetic resonance imaging (MRI) and computed tomography (CT).(72) Measures of muscle thickness using US have also been validated against direct measurements of muscle tissue biopsies of dissected cadavers.(72) An intraclass correlation coefficient (ICC) of 0.97 was found for test-retest ability of US and CT when the RF muscle was measured on two consecutive days by the same investigator.(73) An ICC of 0.92 was found between US and CT during the assessment of RF muscle diameter.(73) Thus, measurements using US or CT scan-based muscle mass analysis of the quadriceps muscle, specifically RF, appears to be equally accurate.(74) The assessment of muscle thickness measured at multiple sites, by means of US and muscle tissue from the same sites, that were dissected from cadavers produced an ICC of >0.968 ($p < 0.001$).(75) This demonstrates the validity of US when compared to other imaging modalities or even physical dissection of muscle tissue.

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US has also been suggested as a method of determining peripheral muscle thickness. Parry et al. (14) and Puthucheary et al. (57) found a strong relationship between measures of muscle function and measures of muscle thickness and echogenicity using US. Measurement of quadriceps muscle layer thickness (QMLT) using US has shown excellent intra- and inter-rater reliability.(72,74) In a study done on healthy participants no statistically significant difference was observed between expert and novice results during testing of QMLT with a confidence interval of -0.067 to -0.011 and a p-value of 0.1607.(74)

US has also been used as a non-invasive, easy to use and rapidly available tool to assess diaphragm structure at patient's bedside. US showed great inter-observer reliability regardless of the expertise level of the tester when assessing the diaphragm and quadriceps muscles.(72) Muscle thickness and echogenicity using either trace or square method had an ICC of between 0.84 to 0.99.(72) More specifically the interobserver reliability for muscle thickness had an ICC of 0.97 for the quadriceps and 0.86 for the diaphragm and echogenicity had an ICC of 0.90 for the quadriceps and 0.85 for the diaphragm in the novice tester group.(72)

3.12.1.2 Peripheral muscle strength:

One of the most widely used methods to assess muscle strength is manual muscle testing by means of the Medical Research Council sum score (MRC-SS). These manual muscle strength assessments are done in standardized positions to ensure the test is reproduced in the same way. The MRC-SS has been shown to have excellent interrater reliability, with an ICC of 0.99 (95% CI).(17) However, the MRC-SS has limitations in detecting less severe muscle weakness and thus has a ceiling effect (32) seeing as when MRC-SS scores ranging from 0 (paralysis) - 5 (normal muscle strength) are greater than a grade 3 (movement against gravity), the MRC-SS loses much of its ability to distinguish between grades of strength.(62)

A more sensitive method of muscle strength testing, especially at grades 4 – 5, is isometric muscle strength testing using HHD.(76) HHD is more sensitive than in the assessment of muscle strength than the MRC-SS.(32) HHD is a reliable measurement of muscle strength in alert critically ill patients.(76) When assessed it showed an interobserver agreement with an ICC of >0.90.(62) HDD can detect muscle weakness

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where the participant is stronger (MRS-SS greater than grade 3). Thus, a combined method of using both MRC-SS and HDD in the assessment of peripheral muscle strength was chosen in this study. This allowed for better detection of muscle weakness even in stronger ICU survivors.

3.12.1.3 Respiratory muscle strength:

A simple and non-invasive method of assessing respiratory muscle strength is by determining maximum respiratory pressures.(77) The most objective way of assessing respiratory muscle strength is by measuring transdiaphragmatic pressure in reaction to phrenic nerve stimulation (PdiTw).(78) This is however an invasive test which is difficult to perform. In a study to determine the correlation between MIP and PdiTw and thus the reliability of MIP, to assess respiratory muscle strength, the values between MIP and PdiTw correlated with each other (r^2 = 0.373, p = <0.001).(79) In this study however, we have chosen to assess respiratory muscle strength by means of MIP as it is a safer less invasive test with minimal risk to the participant.

3.12.1.4 Respiratory muscle endurance:

There is no current measure for respiratory muscle endurance that has been validated within the ICU population. As previously stated, the proposed method was based on similar evaluation of respiratory muscle endurance for COPD patients.(66)

3.12.2 Physical function

3.12.2.1 Performance-based physical function using the CPAx:

The Chelsea critical care physical assessment tool (CPAx) has been found to be reliable and valid for use in the ICU population. The CPAx demonstrated moderate to strong significant positive correlations with the MRC-SS, Glasgow Coma Scale (GCS), sedation score, peak cough flow and Australian therapy outcome measure score using Spearman's rank correlation coefficient analysis.(67) This tool has been considered content valid with a content validity index of 1.00 ($p<0.05$) and had an interrater reliability of k 0.988 (95% CI 0.791 to 1.00; $p<0.01$).(80)

3.12.2.2 Self-report physical function using the BI:

In order to assess physical function at three months follow up, the Barthel Index (BI) was administered telephonically. In a study to determine the reliability and validity of

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the BI administered over the phone compared to in person evaluation, the mean value of the BI score was 30 by telephone and 35 by in person assessment with a p-value of 0.29.(81) Demonstrating that telephonic administration of the BI is reliable in comparison within person evaluation.(81) When evaluating the validity of the BI in relation to the FIM and Modified Rankin Scale (MRS), in stroke patients, the correlation coefficients were 0.9479 ($p<0.0001$) between BI and FIM score and -0.8856 ($p<0.0001$) between BI and MRS.(82) Showing that the three measures are highly correlated.

3.12.3 Exercise tolerance

The six-minute walking distance (6MWD) is a commonly used measure of exercise tolerance in the critically ill population. The 6MWD has been shown to have moderate to strong correlations to physical health measures and good convergent and discriminant validity.(83)

3.12.4 Health related quality of life (HRQoL)

The EQ-5D was chosen for two main reasons: 1) it is available in numerous languages with cultural variations and 2) it addresses multiple domains and factors that could potentially influence long term HRQoL. The EQ-5D was the outcome measure included in the core outcome measurement set, for the HRQoL domain.(3) This outcome measure is also one of the most used tools to measure HRQoL in the critically ill population.(84) The EQ-5D has been proven to have construct validity,(84) criterion validity and reliability.(85)

3.13 Data and Statistical Analysis

All data was captured electronically via Redcap secure web application (86) by the PI. All data collected was de-identified. Each participant was given a number by which their data was stored and accumulated. Only the PI had full access to the data set. The web application was password protected and further access to the data was controlled by the PI.

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IBM SPSS (IBM, USA) version 25 was used to analyse data. Data was tested for normality using the Shapiro-Wilk W-test. Means and standard deviations or medians and interquartile ranges was determined as appropriate for the distribution and used for descriptive purposes.

Preliminary data analysis was done in consultation with a statistician at the Biostatistics Unit, Division of Epidemiology and Biostatistics, Stellenbosch University.

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CHAPTER 4 : RESULTS OF PRIMARY STUDY

In this chapter the results of the primary research study are presented with reference to the study aim.

4.1 Participant flow

In total 91 patients were screened and 21 were enrolled in the study between February and July 2019. Of the included participants five died during ICU. After ICU discharge one participant absconded from hospital care and was only available for follow up of self-reported physical function and HRQoL assessments. In total 15 participants were followed up at three months. Participant flow during this study is represented in Figure *4.1*.

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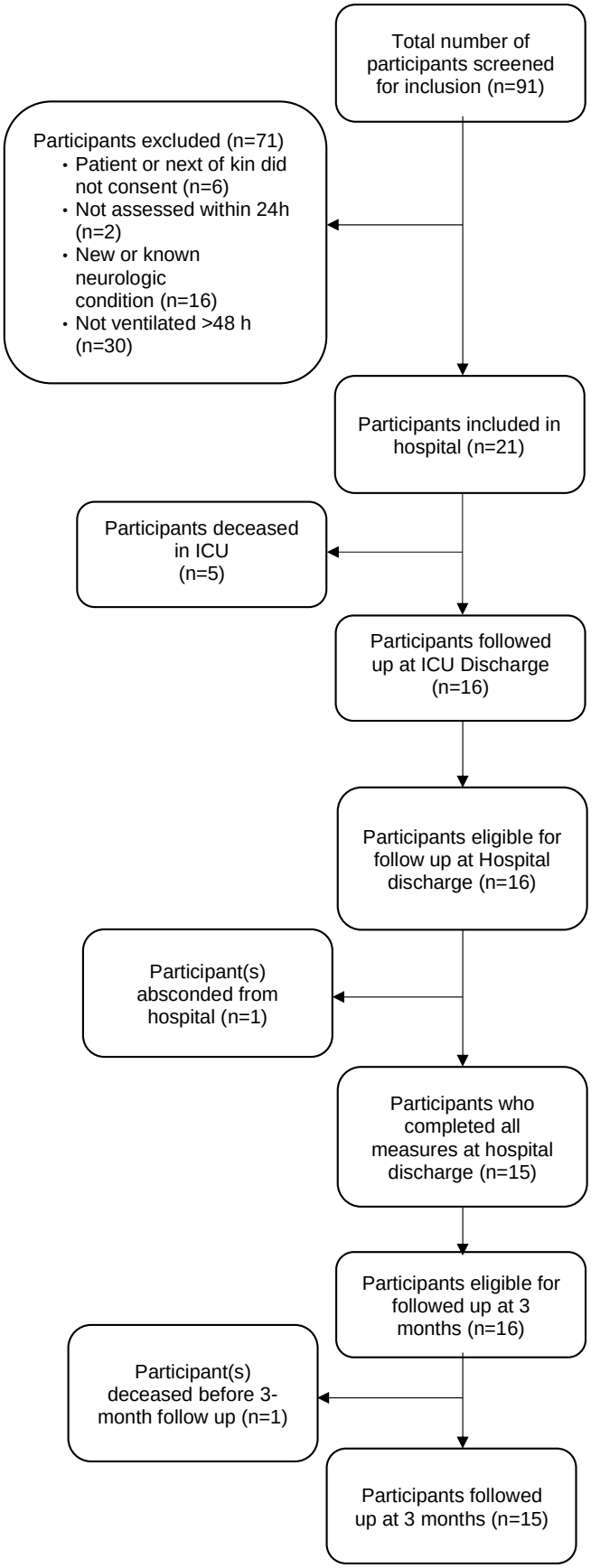

Figure 4.1: **Flow diagram demonstrating participant inclusion**
ICU=intensive care unit.
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4.2 Description of population

4.2.1 Demographic characteristics

Demographic characteristics are presented in Table 4.1. The median age of the participants was 70 (IQR 59-80) years and 11 (52%), of the included participants (n=21), were male. The majority of patients were retired (n=13 [62%]), admitted for medical conditions (n=12 [57%]) and had known diagnosis of hypertension (n=16 [76%]).

Table 4.1: Demographic characteristics of included participants (n=21)

Characteristic	No. %, Unless Otherwise Specified
Age, yr median (IQR)	70 (59-80)
Male	11 (52)
Weight, kg mean (SD)	89 (23)
Height, cm mean (SD)	168 (11)
ETOH	10 (48)
Smoking history	8 (38)
Current	7 (33)
Previous	1 (5)
Employment status	
Employed	7 (33)
Unemployed	1 (5)
Retired	13 (62)
Admission diagnosis	
Medical	12 (57)
Surgical	9 (43)
Co-morbidities	
Hypertension	16 (76)
Cholesterol	7 (33)
Diabetes	8 (38)
COPD	2 (10)
Asthma	3 (14)
IHD	2 (10)
CCF	1 (5)
RA	0 (0)
Past TB	0 (0)
Other	9 (43)
– CA Colon	1 (5)
– Chronic renal failure	1 (5)
– Gout	1 (5)
– Depression and anxiety	1 (5)
– CA Abdomen	1 (5)
– Immunosuppressed	1 (5)
– Depression	1 (5)
– Atrial Fibrillation	1 (5)
– RVD +	1 (5)

COPD= chronic obstructive pulmonary disease; IHD= ischemic heart disease; CCF= congestive cardiac failure; RA= rheumatoid arthritis; TB= tuberculosis.

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4.2.2 Critical illness factors

The individual severity of illness scores, LOV, LOS and mortality are shown in Table 4.2.

The median SAPS 3 score was 57 (IQR 43-67). With eight participants scoring between 40-50 and the majority of participants (n=13 [81%]) scoring above 53 on the SAPS 3. The median LOV was 6 days (IQR 3-10), ICU LOS 13 (IQR 9.5-22) days and total LOS in hospital 19 (IQR 15-26) days. The longest LOS was 37 days in ICU and 47 days in hospital.

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Table 4.2: Severity of illness, LOV, LOS and mortality of included participants (n=21)

Participant	SAPS 3	LOV (days)	ICU LOS (days)	Total LOS (days)	Mortality in hospital	Mortality post discharge
a	40	3	9	20		
b	61	7	13	15		
c	66	6	17	17	√	
d	45	2	2	3	√	
e	71	1	3	3	√	
f	57	4	12	25		
g	67	8	11	19		
h	64	31	31	38		
i	81	14	17	20		
j	40	10	10	10	√	
k	73	5	9	19		
l	85	24	28	40		
m	28	2	37	47		
n	66	6	20	26		
o	44	4	13	16		
p	54	8	8	9	√	
q	32	5	11	15		
r	55	8	24	26		√
s	41	11	30	35		
t	58	9	15	18		
u	48	2	12	19		

SAPS 3= Simplified Acute Physiology Score 3; LOV= length of ventilation; ICU= intensive care unit; LOS= length of stay.

During the first three days of ICU admission the majority of participants received sedation agents (see Table 4.3) and were under deep sedation according to the Richmond agitation and sedation scale (RASS) (Figure *4.2*).

Table 4.3: Medication exposures day 1 to 3 in ICU

	Sedation Agents no. (%)	Corticosteroids no. (%)	NMBA's no. (%)	Glucose control no. (%)
Day 1 (n=21)	21 (100)	6 (29)	2 (10)	12 (57)
Day 2 (n=21)	21 (100)	6 (29)	0 (0)	11 (52)
Day 3 (n=19)	18 (94)	5 (26)	0 (0)	8 (42)

ICU= intensive care unit; NMBA's= Neuromuscular Blocking Agents.

The level of sedation decreased within the first three days of ICU stay and by day three one participant did not receive any sedation. Exposures to medication for the first three days in ICU are shown in Table 4.3.

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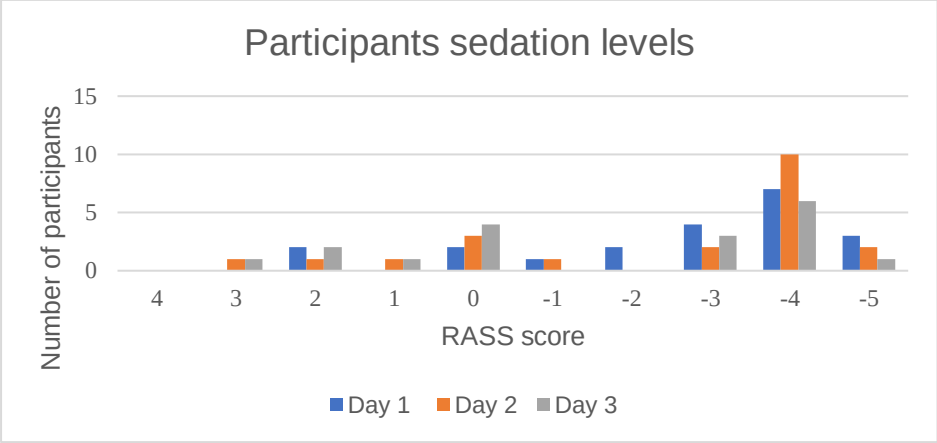

Figure 4.2: **Sedation Levels of participants**
RASS= Richmond agitation and sedation scale.

4.2.3 Return to work

Only two (40%) of the survivors who were previously employed (n=5) returned to work within three months after hospital discharge (see Table 4.4). Both these participants reported that they returned to the same type of work they were performing prior to ICU admission.

4.2.4 Healthcare utilisation

Half of the ICU survivors (n=8 [50%]) were discharged home and just less than half were discharged to a rehabilitation centre (n=7 [44%]). Of the survivors, 8 (50%) received physical rehabilitation after discharge from hospital and 6 (38%) were re-admitted to hospital care. Individual healthcare utilisation is represented in Table 4.4.

4.2.5 Mortality

Mortality in hospital (n=5 [24%]) were all within ICU stay. One participant died prior to telephonic follow up at three months (see Table 4.2).

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Table 4.4: Discharge destination, health care utilisation and return to work of ICU survivors (n=16)

Participant	Discharge Destination	Employment status	Return to work	Re-admission	Physical Rehabilitation
a	Home	Retired		√	
b	Home	Employed	√	√	
f	Home	Unemployed			
g	Rehabilitation Centre	Retired			√
h	Home	Employed			
i	Home	Retired		√	
k	Rehabilitation Centre	Retired			√
l	Rehabilitation Centre	Retired			√
m	Home	Employed			
n	Rehabilitation Centre	Retired		√	√
o	Home	Employed	√		√
q	Step Down Facility	Retired			
r	Home	Employed		√	
s	Rehabilitation Centre	Retired			√
t	Rehabilitation Centre	Retired			√
u	Rehabilitation Centre	Retired		√	√

ICU=intensive care unit.

4.3 Muscle structure and function

4.3.1 Peripheral muscle structure:

The median scores for RF and VI muscle thickness and echogenicity are shown in

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Table 4.5. Median RF and VI echogenicity did seem to increase for the first three days in ICU indicating that muscle quality decreased in this time.

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Table 4.5: Measures of peripheral muscle structure

	RF thickness (cm)	VI thickness (cm)	RF echogenicity (pixels)	VI echogenicity (pixels)
Day 1	0,77 (0,64-0,82)	0,63 (0,54-0,77)	6,56 (4,25-10,14)	2,50 (1,51-5,42)
Day 2	0,75 (0,64-0,83)	0,65 (0,54-0,70)	6,55 (3,43-8,92)	3,63 (1,63-6,84)
Day 3	0,85 (0,69-0,93)	0,74 (0,52-0,80)	7,23 (5,13-8,79)	4,59 (1,84-5,64)
ICU DC	0,79 (0,65-0,94)	0,67 (0,58-0,76)	7,42 (5,73-10,54)	3,68 (2,56-6,19)
Hosp DC	0,77 (0,64-0,91)	0,68 (0,59-0,77)	6,67 (5,83-8,90)	3,05 (2,35-9,23)

Measures presented as Median (IQR). RF=Rectus Femoris; VI=Vastus Intermedius; ICU=intensive care unit, DC= discharge, Hosp= hospital.

Figure *4.3* represents each individual participant's peripheral muscle thickness measures, for both RF and VI, between assessment time points. Between day 1 and day 2 in ICU, 6 (29%) participants demonstrated an increase of more than 10% in RF muscle thickness and 4 (19%) participants demonstrated a decrease of more than 10% (Figure *4.3*). An increase in VI thickness was seen in 7 (33%) participants and a decrease in 8 (38%) participants. Muscle thickness remained unchanged in the RF of 11 (52%) participants and 6 (29%) participants in the VI. The median increase in RF muscle thickness was 22% (IQR 15-37) and the median decrease was 25% (IQR 13-34). The average increase in VI muscle thickness was 17% (IQR 12-65) and the average decrease was 20% (IQR 15-28).

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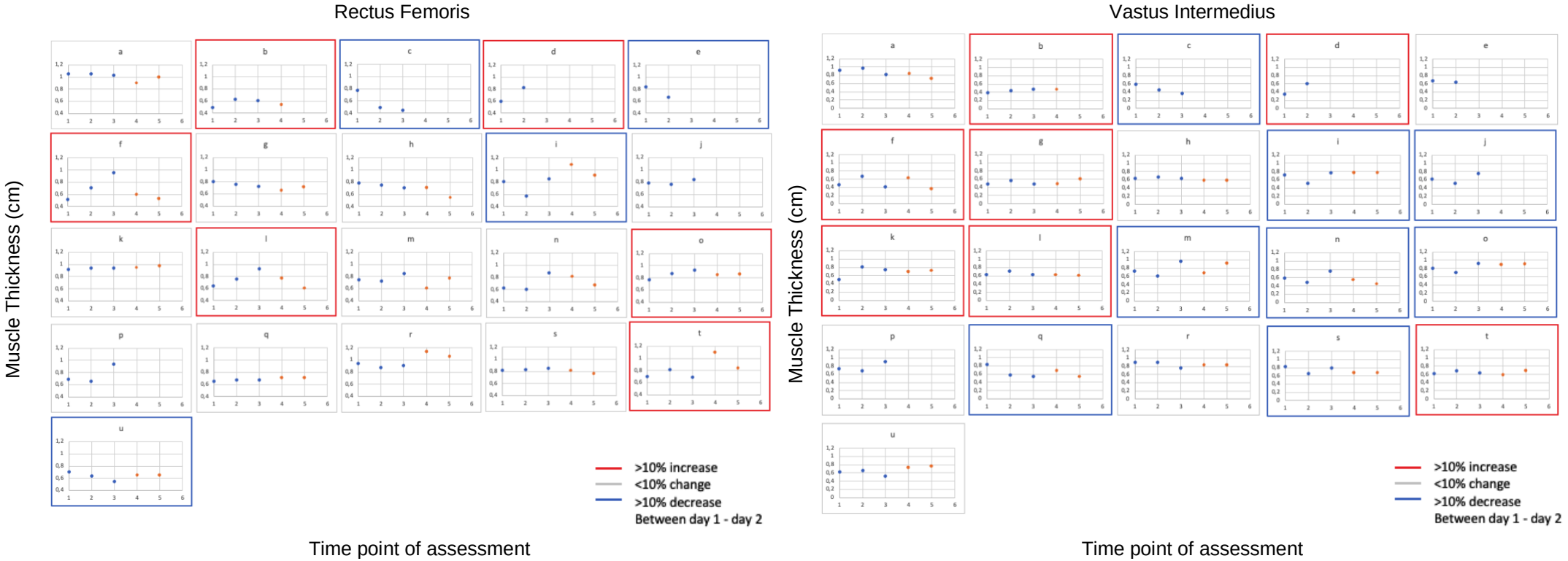

Figure 4.3: **Peripheral muscle thickness by time point of assessment**

This figure represents individual participant data in a panel tabulation format. 1 participant per panel. For each participant, the y-axis represents muscle thickness; and the x-axis is the time point of assessment. 1=Day 1 in the intensive care unit (ICU), 2=Day 2 in ICU, 3=Day 3 in ICU, 4= ICU discharge, 5= hospital. The individual panels highlighted in red represent participants who had an increase in muscle thickness between day 1 and day 2 in ICU, whereas the panels highlighted in blue represent participants whose muscle thickness decreased between day 1 and day 2.

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Figure *4.4* represents each individual participant's peripheral muscle echogenicity, for both RF and VI, measures between assessment time points. Between day 1 and day 2 of ICU admission, 7 (33%) participants demonstrated an increase of more than 10% in RF muscle echogenicity and 11 (52%) participants demonstrated a decrease of more than 10% (Figure *4.4*). An increase in VI echogenicity was seen in 12 (57%) of participants and a decrease in 7 (33%) participants. Muscle echogenicity remained unchanged in the RF of 3 (14%) and 2 (10%) in the VI. The median increase in RF muscle echogenicity was 73% (IQR 26-130) and the average decrease was 51% (IQR 29-65). The average increase in VI muscle echogenicity was 80% (IQR 36-139) and the average decrease was 25% (IQR 12-52)

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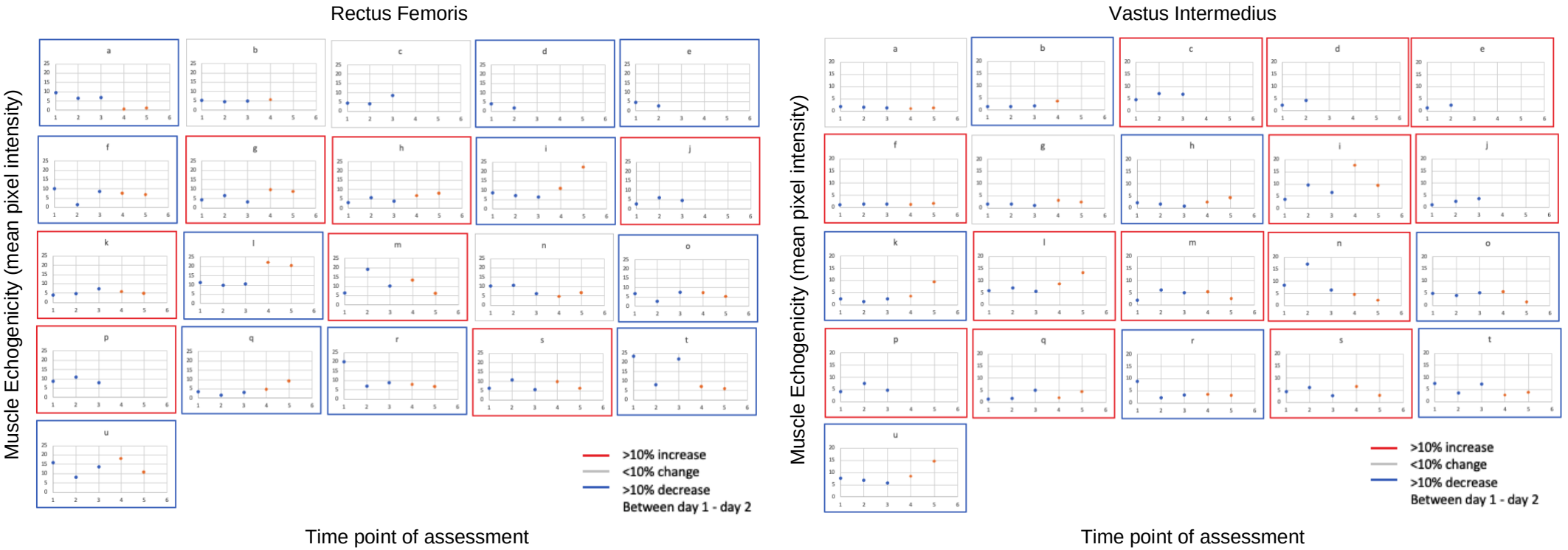

Figure 4.4: **Peripheral muscle echogenicity by time point of assessment**

This figure represents individual participant data in a panel tabulation format. 1 participant per panel. For each participant, the y-axis represents muscle echogenicity; and the x-axis is the time point of assessment. 1=Day 1 in the intensive care unit (ICU), 2=Day 2 in ICU, 3=Day 3 in ICU, 4= ICU discharge, 5= hospital. The individual panels highlighted in red represent participants who had an increase in muscle echogenicity (worsening) between day 1 and day 2 in ICU, whereas the panels highlighted in blue represent participants whose muscle echogenicity decreased between day 1 and day 2.

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4.3.2 Peripheral muscle function:

Individual participant peripheral muscle function scores are represented in Table 4.6.

Median MRC-SS score at ICU discharge was 53 (IQR 42 – 56) and 55 (IQR 41 – 58) at hospital discharge. Of the survivors (n=16), 6 (38%) demonstrated ICU-AW at ICU discharge. Of the participants with ICU-AW (n=6), 4 (67%) still demonstrated ICU-AW at hospital discharge.

The median HHD score for the dominant lower limb was 40% (IQR 33 – 50), of the predicted for age, sex and weight related norms, and 37% (IQR 33 – 45) on the non-dominant lower limb. The median HHD percentage predicted was 57% (IQR 42 – 66) on the dominant upper limb and 52% (IQR 40 – 74) on the non-dominant upper limb. Only 4 participants scored above 50% of the predicted normal values for their dominant lower limb and 10 for their dominant upper limb at hospital discharge.

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Table 4.6: Peripheral and Respiratory muscle function

Participant	Respiratory muscle strength		Respiratory endurance		Peripheral muscle strength					
	MIP (cmH_2O)				MRC-SS (/60)		HHD LL (% predicted)		HHD UL (% predicted)	
	ICU D/C	Hosp D/C	Hosp D/C		ICU D/C	Hosp D/C	Hosp D/C		Hosp D/C	
			Seconds	Breaths			Dom	Non-dom	Dom	Non-dom
a	113	106	52	10	52	59	96	90,2	66,1	87,5
b	61				57					
c	41	43	104	13	55	58	30,9	34,2	69,1	93,3
d	42	33	86	11	**46	55	34,5	34,3	68,3	62,6
e	61	66	52	23	50	51	44,6	42,9	55,5	58,4
f	18	25	63	16	**40	**40	76,8	81,4	68,5	74,1
g	34	51	58	23	54	56	54,1	44,5		50,6
h	19	30	49	23	**34	**40	30,5	29	37,9	31,2
i	47	50	49	16	56	58	29	30,5	42,4	37,9
j	18	25	55	14	**36	**38	39,6	41,6	58,5	45,5
k	23	26	83	19	56	53	39,7	31,5	55,6	38,6
l	34	39	89	14	**46	53	25	25,8	36,5	39,7
m	40	50	55	14	56	58	42,2	37	65,2	78,4
n	13	27	27	8	**37	**41	35,3	34,2	48,1	52,2
o	29	52	86	20	54	56	50,2	45,9	36,7	42,6
p	37	48	35	9	56	56	49,4	53,5	61,6	51,8

***= intensive care unit acquired weakness; MIP= maximal inspiratory pressure; MRC-SS= medical research council sum score; HHD= handheld dynamometry; LL= lower limb; UL=upper limb; ICU= intensive care unit; Hosp= hospital; D/C= discharge; Dom=dominance; Non-dom=non-dominance. We were unable to assess peripheral muscle strength, by means of MRC-SS and HHD, or respiratory muscle strength and endurance for the participant that absconded from hospital care. One other participant was unable to perform HHD for bilateral upper limbs due to a prior orthopaedic injury.*

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4.3.3 Respiratory muscle structure:

The median scores for diaphragm muscle thickness (inspiration and expiration) and Diaphragmatic Thickening Fraction (DTF) are shown in Table 4.7.

Table 4.7: Measures of respiratory muscle structure

Instance	Diaphragm muscle thickness (cm)		DTF (%)
	Inspiration	Expiration	
Day 1 (n=21)	0,25 (0,22-0,26)	0,2 (0,18-0,22)	18,71 (13,83-25,25)
Day 2 (n=21)	0,25 (0,22-0,27)	0,22 (0,17-0,24)	19,12 (12,36-27,76)
Day 3 (n=19)	0,26 (0,24-0,27)	0,22 (0,19-0,23)	17,89 (12,34-26,80)
ICU DC (n=16)	0,26 (0,23-0,28)	0,22 (0,20-0,24)	16,10 (12,16-27,63)
Hosp DC (n=15)	0,25 (0,23 - 0,27)	0,21 (0,18–0,23)	19,75 (12,45-29,47)

DTF= diaphragmatic thickening fraction.

Figure ***4.5*** represents each individual participant's DTF measures between assessment time points. Between day 1 and day 2, 8 (38%) participants demonstrated an increase of more than 10% in DTF (Figure ***4.5***). A decrease of more than 10% in DTF was seen in 10 (48%) participants and in 3 (14%) participants DTF remained unchanged. The median increase in DTF was 90% (IQR 52-155) and the median decrease was 48% (IQR 34-60).

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Figure 4.5: **Diaphragmatic Thickening Fraction (DTF) by time point of assessment**
This figure represents individual participant data in a panel tabulation format. 1 participant per panel. For each participant, the y-axis represents DTF; and the x-axis is the time point of assessment. 1=Day 1 in the intensive care unit (ICU), 2=Day 2 in ICU, 3=Day 3 in ICU, 4= ICU discharge, 5= hospital. The individual panels highlighted in red represent participants who had an increase in DTF between day 1 – 2 in ICU, whereas the panels highlighted in blue represent participants whose DTF decreased.

4.3.4 Respiratory muscle function:

Individual measures for respiratory muscle strength and endurance are represented in Table 4.6.

Median MIP at ICU discharge was 36 cmH_2O (IQR 20 – 46) and 43 cmH_2O (IQR 27 – 51) at hospital discharge. A number of participants had MIP scores below ≥30cmH2O at ICU discharge (n=6 [38%]) and hospital discharge (n=5 [33%]). During respiratory endurance testing the mean time completed was 62.9 (SD 21.9) seconds and in this time an average of 15.5 (SD 5.1) breaths were taken.

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4.4 Physical function

Individual physical function scores by means of CPAx and BI are represented in Table 4.8.

4.4.1 Performance based physical function using the CPAx:

Mean CPAx score at ICU discharge was 36.3 (SD 6.2) and improved to 41.8 (SD 5.1) at hospital discharge. Only one participant scored the highest possible score 50/50 on CPAx, indicating the highest level of independence.

4.4.2 Self report physical function using the BI:

The mean BI score was 80 (IQR 71-94) at hospital discharge. Three participants scored the highest possible score 100/100 on the BI at hospital discharge (see Table 4.8). At three months follow up the median score on the BI was 100 (IQR 95-100).

Table 4.8: Individual scores for physical function, exercise tolerance, and HRQoL

Participant	Exercise tolerance		Physical function				HRQoL
	6MWT		CPAx		BI		EQ-5D
	6MWD (meters)	% predicted					Change
	Hosp D/C		ICU D/C	Hosp D/C	Hosp D/C	3 months	Hosp D/C - 3 months
a	447	69,89	46	50	100	95	Improved
b			46		100	100	Improved
f	117	25,75	40	47	80	100	Improved
g	87	20,4	35	41	80	100	Improved
h	12	2,07	34	38	75	100	Improved
i	120	28,85	39	41	80	100	Improved
k	120	19,44	36	43	80	100	Improved
l	12	2,63	26	32	60	95	Improved
m	60	11,73	35	43	95	100	Mixed
n			30	36	35	25	Worse
o	207	29,85	39	47	85	100	Improved
q	105	18,67	35	43	70	100	Mixed
r	255	34,54	45	48	100		
s			25	35	60	95	Improved
t	60	9,27	34	41	80	100	Improved
u	231	38,21	36	42	90	100	Improved

HRQoL= health related quality of life; 6MWT= six-minute walk test; CPAx= Chelsea critical care physical assessment tool; BI Barthel Index; EQ-5D= EuroQol five dimensions; D/C= discharge.

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4.5 Exercise tolerance

Individual 6MWD and percentage of the predicted normal distance for age, sex and weight is presented in Table 4.8.

Of the 16 survivors, at ICU discharge, only 13 completed the 6MWT. Two participants were unable to walk at the time of hospital discharge and thus could not perform the 6MWT. Of the 13 participants that did complete the test only three were able to perform the tests a second time, as is required according to the ATS guidelines. The reasons for not completing the second test are stated in Figure *4.6*. Of the participants who could perform the test the shortest distance walked in six minutes was 12 meters and the furthest was 447 meters. The median distance walked was 105 meters (IQR 12-207). This was a mean of 20.8% (SD 18.6) of the predicted normal distance. Only one individual participant in this cohort achieved, a distance walked, more than 40% of the predicted value for normal subjects.

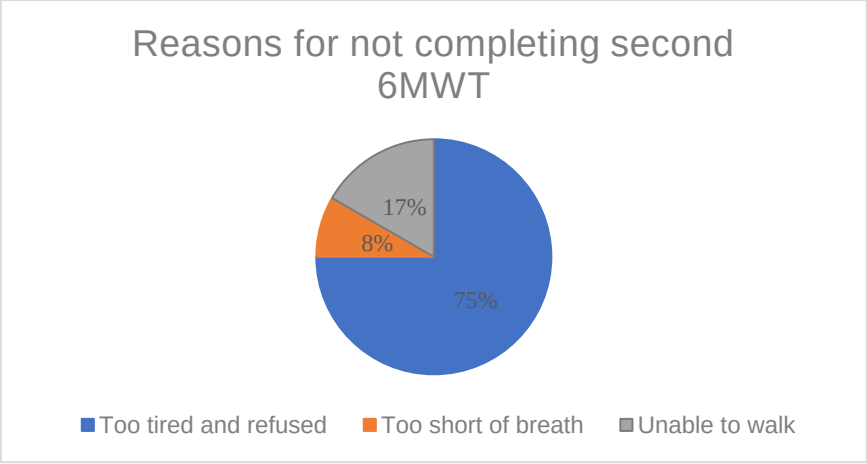

Figure 4.6: **Reason for not completing 6MWT a second time**
6MWT= six-minute walk test.

4.6 Health related quality of life (HRQoL)

The EQ-5D for individual dimension scores, for this patient cohort, at hospital discharge and three months post discharge (follow up) are represented in Table 4.9.

The HRQoL domains most affected (slight problems to severe problems) at hospital discharge were mobility (n=15 [94%]), self-care (n=13 [82%]) and usual activities

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(n=14 [88%]). The domains most affected at three months were mobility (n=6 [40%]), usual activities (n=5 [33%]) and pain or discomfort (n=7 [47%]).

At three months post discharge one participant was still unable to walk, wash or dress, and perform usual activities. At three months post discharge from hospital participants still demonstrated decreased HRQoL.

Using the description of health change, between ICU discharge and three months follow up, the majority of participants (n=12 [80%]) demonstrated better health status, two participants mixed health status, and one participant worse health status (see Table 4.8). The participant who died prior to three months follow up did not have a described change in health status.

The median VAS score at hospital discharge was 60% (IQR 50-78.75) and 80% (IQR 75-85) at three months post discharge. This demonstrates an improvement in overall self-rated health status between hospital discharge and three months follow up.

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Table 4.9: HRQoL dimension scores

Dimension	Hospital D/C no. (%) (n=16)	Follow up no. (%) (n=15)
Mobility		
No problems	1 (6)	9 (60)
Slight problems	8 (50)	5 (33)
Moderate problems	2 (13)	0 (0)
Severe problems	2 (13)	0 (0)
Unable to walk	3 (19)	1 (7)
Self-care		
No problems	2 (13)	12 (80)
Slight problems	8 (50)	2 (13)
Moderate problems	2 (13)	0 (0)
Severe problems	1 (6)	0 (0)
Unable to wash or dress	3 (19)	1 (7)
Usual Activities		
No problems	2 (13)	10 (67)
Slight problems	6 (38)	2 (13)
Moderate problems	1 (6)	2 (13)
Severe problems	2 (13)	0 (0)
Unable to do usual activities	5 (33)	1 (7)
Pain/Discomfort		
No pain/discomfort	7 (44)	8 (53)
Slight pain/discomfort	3 (19)	5 (33)
Moderate pain/discomfort	3 (19)	2 (13)
Severe pain/discomfort	2 (13)	0 (0)
Extreme pain/discomfort	1 (6)	0 (0)
Anxiety/Depression		
Not anxious/depressed	6 (38)	11 (73)
Slightly anxious/depressed	7 (44)	3 (20)
Moderately anxious/depressed	0 (0)	1 (7)
Severely anxious/depressed	2 (13)	0 (0)
Extremely anxious/depressed	1 (6)	0 (0)

HRQoL= health related quality of life; D/C= discharge.

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CHAPTER 5 : DISCUSSION

In this chapter we will discuss, interpret and contextualise the results and statistical analysis as were reported in Chapter 4. We will be discussing the results under the following headings: demographic characteristics, critical illness factors and the following patient outcomes: peripheral and respiratory muscle structure and function, exercise tolerance, physical function, and health related quality of life. To our knowledge this is the first study to report on outcomes of muscle structure and function, during hospital stay and after discharge, of critical illness survivors in the private health care sector of SA.

5.1 Demographic characteristics

When comparing the demographic characteristics of the included participants, the patients in this cohort were older compared to that of other critically ill populations of SA. The age of the participants admitted to another private hospital, in the Gauteng province of SA, was 52 years.(26) The age of publicly admitted critically ill participants, however, ranged between those aged in their 30's,(27,29) 40's (87) and 50's.(28) The median age of the participants in this cohort were thus almost 20 years older than in the critically ill populations previously reported on, in both the private and public health care sectors of South Africa. Further description of specifically privately admitted critically ill participants is needed to see if privately admitted populations are predominantly older than those admitted in the public sector.

The public health sector of South Africa has fewer critical care resources and thus makes use of a triage system to best allocate resources.(24) The private sector ICU bed to total bed ratio in South Africa is 8.9% compared to 1.7% in the public sector.(24) We theorised that the triage system would favour younger adults as their age would relate to better outcomes and lower ICU mortality.

The age of the included private population also accounts for the fact that the majority of participants were retired upon admission. As the mean age was above that of retirement age, of 65 years, in the South African population. In comparison 83% of participants were employed prior to critical illness in the Gauteng province private

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hospital (26) and 52% in a public hospital population of the Western Cape province.(28)

5.2 Critical illness factors

Participants in this cohort were severely ill according to the SAPS 3 scores. With the majority of participants scoring above 53 on the SAPS 3, this being predictive of non-survival, with a specificity of 83% and sensitivity of 75% in a SA population.(24) The high severity of illness scores might have been influenced by the high age and number of co-morbidities of the included critically ill population. Both age and comorbidities form part of the SAPS 3 score calculation to determine severity of illness.(51)

Lower severity of illness scores were reported in other private and public critically ill populations of South Africa.(26–29,87) All these studies however reported severity of illness by means of APACHE II scores.

Given that the participants in this cohort had a higher severity of illness one might expect longer LOV, LOS in ICU and total LOS. However, there did not seem to be a difference in these factors to that of another privately admitted critically ill population of South Africa.(26)

The critical illness factors of LOV, ICU and total LOS were however higher compared to that of most public critically ill populations in SA.(27,28,87) There was however one study performed in the public health sector that reported longer LOS in ICU and hospital, similar to that of the two privately admitted populations.(29) The longer LOS reported by Schneiderman et al. (29) could be accounted for by the fact that this study only included trauma patients and the majority of these were polytrauma admissions. Polytrauma patients tend to score higher on the injury severity scale, the scale being indicative of increased length of stay in trauma patients.(88)

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5.3 Muscle structure and function

5.3.1. Peripheral muscle structure and function:

There is considerable variance to the way in which results on US measures of the peripheral muscles, specifically the RF and VI, are reported in the literature. Very few studies report on mean or median baseline measurements of thickness in these muscles. To our knowledge there is only one study that reported on baseline muscle thickness measures for the RF and VI.(15) Other reports describe change in muscle structure, of the RF and VI, as the percentage change over various time points(15) or the change between measures at two timepoints, described as increase or decrease.(19)

The median baseline measures of RF and VI muscle thickness were less than in the study performed by Parry et al. (15) upon awakening. The participants in the study performed by Parry et al. (15) were younger and less severely ill compared to that of the included participants in this cohort. This could have attributed to the lower muscle thickness measures seen in this cohort.

A decision was made to report on the percentage change in RF and VI muscles between day one in ICU and day two in ICU as change in muscle structure predominantly occurs in the early course of mechanical ventilation.(61) The median percentage change, for those participants who demonstrated a decrease in muscle structure in this cohort, was slightly lower than previously reported. (15) Parry et al. (15) however reported the percentage change of the entire cohort and not just a group of participants. For a large number of participants in this study change in RF and VI thickness remained unchanged.

Puthucheary et al. (54) assessed echogenicity and reported no change in RF echogenicity over time, however, change in RF echogenicity was higher in participants who developed muscle necrosis than in those that did not. Parry et al. (15) reported a 13% increase in RF echogenicity and 25% for VI, indicating worsening muscle quality over time. The median percentage change for the participants in the increase group for both RF and VI was higher in this cohort than previously reported.(15)

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It is important to note that the results in change of muscle structure for both the peripheral and respiratory muscles in this study should be interpreted with caution as the study might not have had adequate power to detect significant change in muscle structure over time, due to its small sample size. Nonetheless, without the establishment of baseline measures or minimal clinically important differences of muscle thickness or muscle echogenicity daily ultrasonography measures in the critically ill population might not currently be of value.

Peripheral muscle weakness was evident in the majority of participants comparted to normative values using HHD, however did not seem to be largely affected on the MRC-SS at hospital discharge. This is in line with literature stating a known limitation of manual muscle testing using the MRC-SS. The MRC-SS has a ceiling effect when attempting to determine less severe muscle weakness.(32) The percentage of predicted normal values for HHD indicates that participants still had peripheral muscle weakness at hospital discharge.

5.3.2 Respiratory muscle structure and function:

A cut-off DFT value of ≥30% has been associated with successful weaning from mechanical ventilation.(59) As seen in this cohort the median DTF values were far below this cut-off value at each time point of assessment. These scores below the cut-off value for DTF, especially at ICU and hospital discharge, when participants were breathing spontaneously, is an indication of poor inhalation effort (89) and possible diaphragmatic dysfunction.(90) We hypothesise that measures of DTF could be indicative of diaphragmatic atrophy and contribute to respiratory muscle weakness.

Results on change in diaphragm structure was reported similar to the methods described by Goligher et al. (61), 44% of participants demonstrated a decrease in DTF and 12% of participants demonstrated an increase in this study. Compared to 38% of participants who demonstrated an increase and 48% of participants who demonstrated a decrease in this study. It is important to note that Goligher et al. (61) reported change over eight days compared to the change between one and two days in this study. Significant change in diaphragm muscle thickness has been reported by Grosu et al. (20) at a rate of 6% per day of mechanical ventilation.

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During assessments of respiratory muscle strength, a large number of participants demonstrated respiratory muscle weakness. As a MIP of below ≥30cmH_2O has been defined as an indication of global inspiratory muscle weakness.(91) This strengthens the hypothesis that the median DTF scores of below 30% could be linked to low respiratory muscle strength measures in these critically ill participants. Very few studies have evaluated respiratory muscle strength by means of MIP in the critically ill population, thus comparison to other critically ill populations is difficult.

It is interesting to see that all participants who demonstrated a low MIP at both ICU and hospital discharge were the same participants identified with ICU-AW at both these time points. This might be an indication that these participants had global muscle weakness.

There is currently no validated measure of assessing respiratory muscle endurance in the critically ill population. To our knowledge the outcome of assessing respiratory muscle function has not frequently been performed in the critically ill population. There are no normative values available for respiratory muscle endurance using the assessment method as described in Chapter 3. Previous studies have however calculated the fatigue resistance index (MIP final/MIP initial) to report respiratory muscle endurance.(18) Unfortunately, in this study we did not perform a measure for maximal inspiratory pressure following the respiratory muscle endurance test and did not calculate the fatigue resistance index. However, the mean time completed during endurance testing in this cohort, was just over one minute. Both the mean time completed for the entire cohort and individual respiratory muscle endurance scores were much lower than the expected 3 to 7 minutes of breathing participants should be able to perform against a resistance of 50 to 60% of MIP.(66) Indicating a decrease in respiratory muscle endurance in these critical illness survivors. A protocol for the assessment of respiratory muscle endurance measurement in the critically ill population and comparison to normal participants requires further investigation.

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5.4 Physical function

5.4.1 Performance-based physical function using the CPAx:

The mean CPAx score at ICU discharge was similar to outcomes reported in a study performed in Soweto, SA.(27) The CPAx scores of participants were only slightly decreased at both time points and demonstrated an improvement between ICU and hospital discharge for all participants. The CPAx score was however still decreased for all but one participant at hospital discharge.

In a study performed by Corner et al. (80) median CPAx scores similar to that of the participants in this study was indicative of a survival category of discharge home with community support. This community support is defined as the need for a package of care which could include outpatient therapy or home-based therapy.(80) In this study however, seven of the survivors required the need for additional in-patient physical rehabilitation following discharge. Thus most of the participants in this study were in the survival category similar to those discharged to short stay rehabilitation and not discharge home.(80) The utility of the CPAx in a SA population requires further investigation.

5.4.2 Self-reported physical function using the BI:

The self-report physical function scores on the BI were only slightly decreased at hospital discharge, but at three months follow up the BI scores for the majority of survivors were not decreased at all. These scores were based on participants' ability to perform ADL's. Future studies might want to consider using another self-report measure of physical function at follow up post discharge. As the BI has a known ceiling effect and might not have discriminated between patients scoring at the higher range of the index.(82,92)

Given the evident respiratory and peripheral muscle weakness participants performed better than expected during assessments of physical function, both self-reported and performance-based. We hypothesise that self-report physical function might have been exaggerated at three months follow up explaining the high scores in this particular outcome compared to those reported in another study.(32)

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Future studies might find it beneficial to obtain retrospective measures of physical function to determine a baseline level of activity and general performance of ADL's in comparison to assessing physical function after critical illness. Retrospective measures of physical function have been performed, using level of independence with ADL's as scored by the Katz Index of ADL's or highest level of mobility as scored with the IMS.(47)

5.5 Exercise tolerance

Exercise tolerance, a measure of functional exercise capacity, was reduced at hospital discharge. Exercise tolerance was assessed by means of the 6MWT determining 6MWD and comparing these to predicted normal values for age and sex matched controls. The poor performance of participants during the 6MWT could be due to several contributing factors such as the evident peripheral and respiratory muscle weakness and decreased respiratory muscle endurance.

The mean distance walked in six-minutes at hospital discharge was similar to that of an Australian population at ICU discharge.(93) Studies evaluating exercise tolerance long term have reported that the exercise capacity of survivors improve over time but at 12 months was still lower than the predicted normal values.(94) Participants followed up at three months, by Herridge et al. (94) were only able to walk 49% of the predicted normal values.(94). In this study we unfortunately did not re-assess exercise tolerance at three months. Thus, the long-term outcomes in exercise tolerance and performance based physical function is unknown.

5.6 Health related quality of life (HRQoL)

The median overall self-rated health status at hospital discharge, by means of the EQ-5D VAS score, demonstrated a decreased HRQoL at this time point. (71) The self-rated health status did however improve within the three months following hospital discharge, similar to that of privately admitted critically ill participants in Gauteng.(26) Van Aartsen and Van Aswegen (26) followed participants up until six months following hospital discharge and the overall self-rated health status seemed to further improve within this timeframe. Another study performed in Johannesburg South Africa in a

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public hospital demonstrated lower self-rated health status, than that of privately admitted patients, at 6 months following discharge from a trauma ICU.(29)

In other studies participants also had higher or near normal health related quality of life, after discharge from ICU, but then demonstrated a decrease in the longer term. Cuthbertson et al. (13) reported that the physical domain of participants' quality of life returned to pre-morbid levels within 12 months from ICU discharge but then decreased again between 2.5 to 5 years.

The HRQoL domains most affected at hospital discharge were usual activities, mobility and self-care. The domains most affected at three months were pain or discomfort, mobility and usual activities. This corresponds to domains which were affected at one month follow up in another SA critically ill population.(26) Interestingly these domains correspond to both the performance of specific activities and ADL's, strengthening the hypothesis participants might have had limitations in physical function that were not evident by their BI scores. The domains reported to still be affected at six months post discharge in other SA critically ill populations were pain or discomfort, anxiety or depression, and usual activities.(26,29) Outcomes in the domains of pain or discomfort and anxiety or depression seem to remain affected in the longer term. Whether these domains remain affected and to what extent HRQoL is affected, in the SA population, in the long term requires further investigation.

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CHAPTER 6 : CONCLUSION

The objective of this chapter is to highlight the final conclusions drawn from the results, statistical analysis and their context as provided in Chapter 5. In this chapter we will also describe the study limitations and make recommendations for future research.

6.1 Conclusion

Our study contributed to the very limited information on baseline demographic and critical illness factors available on the critically ill population of SA, specifically that of the private health care sector. Privately admitted critically ill participants differ in both the baseline characteristics and critical illness factors compared to that of publicly admitted critically ill patients. Private critically ill patients tend to be of an older age and more severely critically ill. Whether resource allocation plays a role on these specific factors when compared to the public sector population is unknown.

The average age of participants in this population was well over that of retirement age in SA, in this population return to work was included as a purely descriptive outcome in order to describe HRQoL and build on the baseline data of other SA critically ill populations.

The age and severity of illness of participants could account for the differences in muscle structure seen in this cohort, compared to those previously investigated. However, currently the assessment of outcomes in peripheral muscle structure do not seem be of value. Without the establishment of baseline measures or minimal clinically important differences of peripheral muscle thickness and muscle echogenicity daily ultrasonography measures in the critically ill population are difficult to put into context. Further investigation with larger sample sizes is required in the investigation of muscle structure within the critically ill population.

For measures with established normative values, 6MWT and HHD, participants demonstrated largely decreased muscle strength and exercise tolerance in this cohort. These outcomes were not evident using manual muscle testing and measures of performance based or self-report physical function. Manual muscle testing did

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however assist in identifying participants with ICU-AW. Participants with ICU-AW also demonstrated low respiratory muscle strength and impaired respiratory endurance.

Even though, physical function of participants was not largely affected at hospital discharge or at three months follow up, assessments of HRQoL did reveal that participants still had problems in the domains of mobility and usual activities.

6.2 Limitations

This study had a number of limitations. The first of which is that it took place in only one study site, a private hospital, in SA. This limitation exists as there was limited monetary and research staff resources. This study does thus not represent the entirety of the SA critically ill population.

This study included a small sample size. Thus, the reported statistical changes in specifically peripheral and respiratory muscle structure need to be interpreted with caution. These results within a larger patient population might differ. The small sample size was pre-empted prior to the commencement of this study and thus no statistical correlations between outcomes were attempted, only descriptive statistics on the various patient outcomes.

Another limitation is the possibility of confirmation bias as the PI collected the data and analysed the results. This might have led to unconscious bias during the interpretation of the study results. This bias was addressed to some extent by including outcome measures that have described protocols and performing the data analysis on deidentified information. This might have been avoided in totality by the use of an independent assessor.

Lastly limitations existed in some of the chosen outcome measures used as tools during the assessments undertaken in this population. As stated in Chapter 3 the MRC-SS as a method of manual muscle strength testing has a known ceiling effect that could lead to less severe muscle weakness not being identified (62). This

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particular limitation was addressed prior to study commencement by including a second measure of muscle strength assessment at hospital discharge.

The assessment of physical function using both the BI and CPAx demonstrated limitations in this patient population. The BI has a known ceiling effect (92) and the potential for exaggeration bias. This bias exists as the BI is a measure of self-reported physical function. Participants could embellish their physical function as more significant than it actually is. At hospital discharge the BI was not the only measure used to assess physical function, but at three months follow up took place telephonically, we did not have a performance-based measure of physical function post discharge.

The limitations of the CPAx to accurately determine patients discharge destination and rehabilitation needs, in a SA critically ill cohort, following discharge require further investigation. Future research should consider including another outcome measure of performance-based physical function within hospital stay.

Exaggeration bias is also possible during the assessment of HRQoL using the EQ-5D. This could explain the high self-rated health status, via EQ-5D VAS score, at three months post discharge from hospital within this population. The short term of follow up of HRQoL measures is also a potential limitation as previous studies have reported decreased HRQoL at one year follow up even though short-term measures were near normal,(13) as is seen in this cohort.

6.3 Suggestions for future research

It is our suggestion that future research be continued in the field of outcomes within the critically ill population of South Africa. Research is needed specifically in the public health care sector of SA. To assist in the expansion of our knowledge on the outcomes of both public and private the critically ill populations in SA. This will allow for the further description of baseline characteristics, critical illness factors and patient outcomes within this field of study and confirm possible discrepancies between the critically ill populations of the private and public health care sectors.

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Furthermore, future studies should aim at including larger sample sizes to allow for accurately powered statistical analysis and a more statistically conclusive description of change in muscle structure over time. Studies with larger sample sizes should also investigate possible correlations between patient outcomes, which has yet to be investigated in the SA critically ill population.

It might also be beneficial when conducting research on outcomes such as physical function and health related quality of life to use both a self-report and performance-based outcome measurement tool to avoid potential recollection bias. Future research should attempt to investigate the validity of outcome measures of specifically physical function and HRQoL in the SA critically ill populations.

The long-term outcomes of critical illness survivors in SA are unknown and thus require future investigation. Further investigation and comparison to that of international critically ill populations. In addition, the data is needed to determine the burden of ICU survivorship on the SA healthcare system and identify optimal rehabilitation strategies to manage ICU survivors.

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ADDENDA

ADDENDUM A : Author guidelines Springer Intensive Care Medicine

Intensive Care Medicine
Journal home
Submission guidelines

Submission guidelines

Contents

Instructions for Authors

General

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• Conclusions are presented in a clear and concise manner and are supported by the data.
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- Contributed substantially to the conception and design of the study, the acquisition of data, or the analysis and interpretation of the data.
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Types of Papers
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Original Papers

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• According to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, designation as an author must satisfy three conditions. Each author must have:
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• Proposals for review articles should be submitted as a two-page outline so that content can be discussed at an early stage. Review articles must include original tables, figures, graphs, and other didactic materials. They must provide unique information not available elsewhere.
• Authorship should comply with the ICMJE recommendation for authorship and the role of each author should be specified in the first page of the manuscript below the byline.
• At the Editor's decision, authors may be asked to reduce the number of authors in the byline whenever appropriate. The authors may add a study group name as an author in the byline and list the study group members in an appropriate footnote in the first page of the manuscript in order to have their names entered in PubMed as Collaborators.
• In addition to the abovementioned statements an Authorship and Conflict of Interest form should be completed, signed by each author and uploaded with the manuscript. The form can be downloaded below.
• Authors of original papers and reviews are requested to provide the following information:
- A "Take-home message" (two sentences) which summarizes how the manuscript adds to current knowledge. This will appear in the final published version of the paper.
- A 140-character Tweet that may appear online via the Intensive Care Medicine website or social media platforms. This Tweet will not form part of the print version of the manuscript
Two types of reviews are considered: Systematic Reviews and Meta-Analyses (or a combination of both). It is strongly recommended that systematic reviews and meta-analyses comply with the PRISMA Statement, which is available
here
Conflict of Interest form (Download pdf, 162 kB)
Narrative/Scoping Reviews
Narrative/Scoping Reviews should only be submitted after prior consultation with the Editors and are subject to the peer-review process. They represent the state-of-the-art in a specific field of research and are prepared by senior authors with a broad knowledge of the field.
• Narrative reviews should not exceed 4,000 words and 80 references and should contain figures and tables
• Authorship should not exceed 3 authors, preferably from different centres/countries, although some exceptions can be made by the Editors on a case by case basis depending on the topic
• A statement detailing each Author's role in the study and conflict of interest is mandatory for all papers
• In addition to the abovementioned statements an Authorship and Conflict of Interest form should be completed, signed by each author and uploaded with the manuscript. The form can be downloaded below.

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• IRB/ethical committee approval and informed consent statements are not required
• A structured abstract is not required

Conflict of Interest form (Download pdf, 162 kB)

Editorials

• Editorials are always commissioned by the Editors and comment on one or more articles in the same issue of the Journal. Editorials must not exceed 1,000 words and up to 15 references, and include a mandatory table or figure.
• Editorials have a maximum of 3 authors
• No abstract
• Conflict of interest disclosure is mandatory for all papers
• Conflict of interest disclosure is mandatory for all papers and should be accompanied by a form to be signed by each author. The form can be downloaded below.

Letters to the Editor

• Letters to the editor provide an opportunity to present results of high scientific value where a short format is most appropriate. Typically, letters are dedicated to small pilot/feasibility studies and/or preliminary data. They must not exceed 500 words, 5 references and 1 figure or table.
• The journal does not consider case reports or brief reports for publication.
• Authorship of letters to the editor should be limited to 5 authors or less. In case of letters which stem from an original study with a higher number of authors, a choice must be made by the authors on the names that should appear in the byline and those that may appear in a footnote or in a study group
• Study group collaborating authors should be included in the front page but separate from the byline
• To the Editor's discretion the authors may be asked to specify the role of each author in the article preparation

From the Inside

• From the inside includes poetry, trivia, personal stories, thoughts and memories, sounding boards, obituaries or other qualitative materials that authors wish to share with colleagues.

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ADDENDUM B : Search Strategy

DATABASES SEARCHED

PUBMED

Limits applied to database:
Searches in title or abstract
Language: English

Search Terms	Hits
1. ("critical illness" OR critical illness OR critical illness [MeSH]) AND ("physical function" OR physical function OR physical function [MeSH])	124
2. #1 AND ("cardiopulmonary vascular" OR cardiopulmonary vascular OR cardiopulmonary vascular [MeSH]) OR (cardiopulmonary OR cardiopulmonary [MeSH]) OR (cardiovascular OR cardiovascular [MeSH]) OR (pulmonary OR pulmonary [MeSH])	12
3. #1 AND (neuromusculoskeletal) OR neuromusculoskeletal [MeSH]) OR neuromuscular OR neuromuscular [MeSH])	16
4. #1 AND psychological OR psychological [MeSH]	11
5. #1 OR #2 OR #3 OR #4	124
TOTAL	**287**

SCOPUS

Limits applied to database:
Document type article and review
Language: English

Search Terms	Hits
"critical illness" AND "physical function" AND ("cardiopulmonary vascular" OR cardiopulmonary OR cardiovascular OR pulmonary) AND (neuromusculoskeletal OR neuromuscular) AND (psychological) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re"))	75
TOTAL	**75**

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WEB OF SCIENCE

Limits applied to database:
Searches in topics and titles from all databases
Language: English

Search Terms	Hits
1. "critical illness" AND "physical function"	164
2. #1 AND ("cardiopulmonary vascular" OR cardiopulmonary OR cardiovascular OR (pulmonary OR pulmonary)	27
3. #1 AND (neuromusculoskeletal OR neuromuscular)	20
4. #1 AND psychological	18
5. #1 OR #2 OR #3 OR #4	164
TOTAL	**393**

SCIENCE DIRECT

Limits applied to database:
Advanced search
Searches in abstract, title and keywords

Search Terms	Hits
1. “critical illness" AND "physical function" AND ("cardiopulmonary vascular" OR cardiopulmonary OR cardiovascular OR pulmonary) AND (neuromusculoskeletal OR neuromuscular) AND psychological	73
TOTAL	**73**

MEDLINE via EBSCOhost

Limits applied to database:
Searches in title, abstract and word in subject heading
Language: English

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Search Terms	Hits
1. ("critical illness" AND "physical function") OR ("critical illness" AND "physical function") OR ("critical illness" AND "physical function")	74
2. #1 AND ("cardiopulmonary vascular" OR cardiopulmonary OR cardiovascular OR pulmonary) OR AB ("cardiopulmonary vascular" OR cardiopulmonary OR cardiovascular OR pulmonary) OR ("cardiopulmonary vascular" OR cardiopulmonary OR cardiovascular OR pulmonary)	6
3. #1 AND neuromusculoskeletal OR neuromuscular) OR (neuromusculoskeletal OR neuromuscular) OR (neuromusculoskeletal OR neuromuscular)	13
4. #1 AND psychological	11
5. #2 OR #3 OR #4	26
TOTAL	**130**

CINAHL via EBSCOhost

Limits applied to database:
Searches in title, abstract and word in subject heading
Language: English

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Search Terms	Hits
1. ("critical illness" AND "physical function")	49
2. #1 AND ("cardiopulmonary vascular" OR cardiopulmonary OR cardiovascular OR pulmonary)	2
3. #1 AND (neuromusculoskeletal OR neuromuscular)	10
4. #1 AND psychological OR AB psychological OR MW psychological	6
5. #2 OR #3 OR #4	49
TOTAL	**116**

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ADDENDUM C : Duplicate Elimination

Database	Total Hits	Total hits after duplicate elimination
Pubmed	287	**315**
Scopus	75	
Web of Science	393	
Science Direct	73	
Medline	130	
CINAHL	116	
TOTAL	**1074**	

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ADDENDUM D : Ethics approval S16/09/173A

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Approval Letter
Progress Report

10/06/2020

Project ID: 3665

Ethics Reference No: S16/09/173A

Project Title: The impact of critical illness on muscle structure, strength and physical capability

Dear Dr. Alison Lupton-Smith

We refer to your request for an extension/annual renewal of ethics approval received 01/06/2020.

The Health Research Ethics Committee reviewed and approved the annual progress report through an expedited review process.

The approval of this project is extended for a further year.

Approval date: 10 June 2020

Expiry date: 09 June 2021

Kindly be reminded to submit progress reports two (2) months before expiry date.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your Project Id 3665 and ethics reference number S16/09/173A on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mrs. Melody Shana
Coordinator: Health Research Ethics Committee 1

National Health Research Ethics Council (NHREC) Registration Number:
REC-130408-012 (HREC1)•REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)•IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; the South African Department of Health (2006).Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

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ADDENDUM E : Ethics approval S18/08/176

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Health Research Ethics Committee (HREC)

Approval Notice

New Application

11/10/2018

Project ID : 8207

HREC Reference #: S18/08/176

Title: The Outcomes of Privately Admitted Intensive Care Unit Patients up to Three Months Post Discharge

Dear Miss Helena Pool,

The **New Application** received on 29/08/2018 15:45 was reviewed by members of **Health Research Ethics Committee 2 (HREC2)** via **expedited** review procedures on 11/10/2018 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: **This project has approval for 12 months from the date of this letter.**

Please remember to use your **Project ID [8207]** on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Departement of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/8207

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mr. Francis Masiye,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

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Approval Letter
Progress Report

26/08/2019

Project ID: 8207

Ethics Reference No: S18/08/176

Project Title: Effect of timing of source control on outcomes in acute appendicitis

Dear Miss Helena Pool,

Your request for extension/annual renewal of ethics approval dated 16/08/2019 15:26 refers.

The Health Research Ethics Committee reviewed and approved the annual progress report through an expedited review process.

The approval of this project is extended for a further year.

Approval date: 26 August 2019

Expiry date: 25 August 2020

Kindly be reminded to submit progress reports two (2) months before expiry date.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your Project ID **[8207]** and ethics reference number **[S18/08/176]** on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mr. Francis Masiye,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:
REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; the South African Department of Health (2006).Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

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ADDENDUM F : Institutional approval from study site

MEDICLINIC

MEDICLINIC CORPORATE OFFICE
25 DU TOIT STREET
STELLENBOSCH
7600
SOUTH AFRICA

PO BOX 456
STELLENBOSCH
7599
SOUTH AFRICA

T +27 21 809 6500

www.mediclinic.co.za

05 December 2018

Ms HA Pool
52 Arum Estate
George Street
Strand
7130

poolhelanie@yahoo.com

Dear Ms Pool

PERMISSION TO CONDUCT RESEARCH AT MEDICLINIC VERGELEGEN

Your research proposal entitled "The outcome of privately admitted Intensive Care Unite patients up to three months post discharge" refers.

It is in order for you to conduct your research at Mediclinic Vergelegen, and I wish you success with this project.

Yours sincerely

Dr Chris du Plessis
General Manager Clinical Services
MEDICLINIC SOUTHERN AFRICA

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ADDENDUM G : Participant information leaflet and informed consent

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:

The outcomes of privately admitted intensive care unit patients up to three months post discharge.

REFERENCE NUMBER:

PRINCIPAL INVESTIGATOR: Miss Helanie Pool

ADDRESS: Division Physiotherapy, Faculty of Interdisciplinary Health Sciences, University of Stellenbosch, Tygerberg Campus, Western Cape

CONTACT NUMBER: 0733874888

You are being invited to take part in a research project. Please take some time to read the information presented here, which explains the details of this project. The study staff or doctor will answer any questions you may have about this project that you do not fully understand. It is important that you understand what this research entails and how you could be involved. Also, your participation is entirely voluntary. If you say no, this will not affect you in any way whatsoever. You are also free to stop participating in this study at any stage, even if you do agree to take part.

This study has been approved by the Health Research Ethics Committee at Stellenbosch University and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

- Aim

This study will look at how well people that have been in hospital and connected to a machine that helps you breathe (ventilator), for more than one day, recover within three months after they leave the hospital.

- Setting

This study will take place at the intensive care units at Vergelegen Mediclinic (VMC). Critical care unit F (FICU), Cardiology critical care unit N (NICU) and Cardiothoracic critical care unit M (MICU). We hope to recruit 39 people to be part of the study during their hospital stay.

- Procedure

Information like your age, gender, diagnosis, date you were connected to the breathing machine, number of days connected to the machine, medication you received, settings of the breathing machine, number of days in ICU, number of days in hospital and blood results will be collected by the researcher.
During your time in the ICU: We will be measuring your breathing muscle (diaphragm) and the main muscle on the front of your thigh (quadriceps) by using an ultrasound

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machine. This will be done on the first three days of your stay in ICU and repeated the day you leave the ICU and at the time you leave the hospital.
You will be positioned in your bed with your head up. The researcher will find your rib space and place the ultrasound probe with ultrasound gel in these spaces, to see the breathing muscle. Pictures will be taken while you breathe in and out for three breaths. For the thigh muscle you will be lying on your back in your bed with your knee completely straight. A point two thirds between your hip (pelvis) and knee cap (on your thigh) will be identified, where the ultrasound probe with ultrasound gel will be placed to see the muscle and a picture will be taken. You will not feel any pain when the researcher takes these pictures.
The day you leave the ICU to the general ward the following tests will be done:

- Breathing (respiratory) muscle strength test: You will be positioned in bed with your head up. You will be asked to breathe out as far as you can and then take a breath as deep as possible through a machine with a mouth piece. You will rest for two minutes, and then be asked to do this again. This will be done three times to find the best value of your strength. These measures are risk free, but you might feel dizzy after you have done the breaths. This will be tested again the day you leave the hospital.
- Arm and leg muscle strength test: The researcher will ask you to resist certain movements of your arms and then your legs. The arm movements are: lifting your arm to the side and front, bending and straightening your elbow and bending and straightening your wrist. The leg movements are: bending and straightening your hip, bending and straightening your knee, and bending and straightening your ankle. The researcher will be positioning you comfortably for each of these assessments in a standard way.
- Physical function test: To test how well you have recovered in terms of everyday activities we use a tool called the CPAx. The activities we test are: how you breathe, cough, move in the bed, go from lying on your back to sitting on the edge of the bed, moving while sitting, standing balance, sit to stand, moving from the bed to a chair, stepping and grip strength. You do not have to be able to do all of these activities and we will help you if we need to, you will only be asked to perform the ones you can. You will be given clear instructions for each activity.

The day you leave the hospital the following test will be done:

- Arm and leg muscle strength test: The researcher will show you how to perform two movements, one for your shoulder (lifting your shoulder to the side) and one for your knee (straightening your knee). After this has been demonstrated you will be asked to perform these movements against a small electronic machine. This machine measures how much pressure you give when doing these movements. This will be tested when you are discharged from the hospital.
- Respiratory (breathing) muscle endurance: You will be sitting with your arms supported. The researcher will assess your breathing muscle endurance with a machine you place in your mouth. This machine will give resistance while you breathe in. You will be asked to breathe in and out through the machine for as long as you can. The researcher will measure how long you are able to continue breathing and how many breaths you take in this time. You may feel tired or dizzy during this test, but it is not painful.
- Physical function test: The Barthel Index This form asks about how much help you need with activities like going to the bathroom, grooming, using the toilet, eating, moving, dressing, climbing stairs and bathing.

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We will be phoning you three months after you have left the hospital and you will be asked the same questions again.

- Exercise tolerance (how well you can tolerate exercise): You will be wearing comfortable clothes and shoes and use your normal walking aids if you are using any. During this test we will see how far you can walk in six (6) minutes. You can walk as fast as you want during the test and take as many breaks as you need. We will ask you how breathless you feel before and after the test. We will also measure your heart rate, blood pressure and oxygen levels before, during and after the test.
- Quality of life assessment and physical function test: We are going to ask you some questions about things you do in the day and what you think of your health. We will ask about how easily you can move and look after yourself. We will also ask if you have any pain or feel down or anxious. We will also ask you to give your health on the day a mark out of 100. The second form asks about how much help you need with activities like going to the bathroom, using the toilet, eating, moving, dressing, climbing stairs and bathing.

We will be phoning you three months after you have left the hospital and you will be asked the same questions again.

Three months after you have left the hospital we will be phoning you:
We will need to record your phone number so that in three (3) months' time we can phone you. When we phone you, we will ask the same questions about your regular activities and what you think of your health. We will also ask about your need to visit the hospital or if you were re-admitted to the hospital in that time. We will also ask whether you have returned back to your normal work.

Why have you been invited to participate?

- People admitted to an ICU sometimes get so weak after they are discharged that they struggle to return to everyday activities once they are sent home. This study will look at this weakness. It will also tell us what happens when these people go to a general ward, when they are discharged from hospital and how they recover in the following three months once they go home. This can help us to identify people that have a higher risk of becoming weak while they are in ICU and help to find ways to improve treatment that might prevent weakness and long stays in the ICU.

What will your responsibilities be?

- You as participant will be asked to stay relaxed and report any pain or discomfort during any of the tests we perform.
- During the ultrasound measurements you will have to lie still and breathe normally. When the strength measurements are done, you will be asked to stay calm and take the deepest possible breath you can. After this you can rest and recover. You will be asked to sign informed consent to take part in the study. You can stop taking part in this study at any time and this will not change the care you receive.

Will you benefit from taking part in this research?

- You will not benefit directly from this study, but in the future people may benefit from the results. These results will help future studies to identify people at high-risk to prevent weakness due to illness and ventilation.

Are there risks involved in taking part in this research?

- There are no risks involved in the ultrasound tests done in the ICU, the Barthel Index of your physical function or the quality of life test of the EQ-5D. During strength tests of your arms and legs, exercise tolerance, physical function using the CPAx tool

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and the breathing muscle tests you might experience shortness of breath or feel tired. We will make sure there are monitors for that and oxygen for you if there are any signs of distress or discomfort. We will also inform a doctor if you become uncomfortable to ensure you are checked and taken care of. These tests are routine and are mainly risk-free.

If you do not agree to take part, what alternatives do you have?

- Standard care will continue as per normal, for all patients. This study does not involve treatment.

Who will have access to your medical records?

- All data will be kept confidential and saved on an electronic database called Redcap. Each participant will have a study number and only the researcher and research assistant will have access to personal information such as your phone number. This is so that she can contact you again after three (3) months. The results will be published in a thesis and a publication where all the information will remain anonymous (no one will know the information belongs to you). Members of the Ethical committee may need to inspect research records for auditing purposes.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

- In the rare event of any injury occurring during this study, the team of health professionals in the ward will act immediately as needed. You as participant are covered by the insurance of the University of Stellenbosch.

Will you be paid to take part in this study and are there any costs involved?

- No you will not be paid to take part in the study and there will be no costs, if you do take part.
- Participation in this study does not cover any of the costs related to your admission and medical management.
- It is important to note that you (or your medical) are still responsible for the costs related to your healthcare and the current admission.

Can we contact you for future research studies related to your hospital stay?

Yes No

Is there anything else that you should know or do?

- You can contact Helanie Pool on 0733874888 if you have any questions or encounter any problems.
- You can contact the Health Research Ethics Committee at 021-938 9207 if you have any concerns or complaints that have not been helped with by your study researcher.
- You will receive a copy of this information and consent form for your own records.

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Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled: The outcomes of privately admitted intensive care unit patients up to three months post discharge.

I declare that:

- I have read or had this information and the consent form read to me and it is written in a language which I am fluent and comfortable with.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is voluntary and I have not been pressured to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (place) .....…..…….. on (date) ……...…….. 2018.

Signature of participant Signature of witness

Declaration by investigator

I (name) ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use a interpreter. (If an interpreter is used then the interpreter must sign the declaration below.

Signed at (place) .....…..…….. on (date) ……...…….. 2005.

Signature of investigator Signature of witness

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Declaration by interpreter

I (name) ……..…… declare that:

- I assisted the investigator (name) ……. to explain the information in this document to (name of participant) ……..…….. using the language medium of Afrikaans/Xhosa.
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (place) .....…..……. on (date) ……...……..

Signature of interpreter Signature of witness

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ADDENDUM H : Data capture sheet

Confidential

DEMOGRAPHICS

Record ID	_____
Gender	◯ Male ◯ Female
Date of Birth	_____
Date of Assessment	_____
Age	_____
ID number	_____
Weight	_____
Length	_____
Telephone number	_____
Alternative Telephone Number	_____
Employment Status	◯ Employed ◯ Unemployed ◯ Retired
Date of Admission	_____
Date of Admission to ICU	_____
Transferred from another hospital?	◯ Yes ◯ No
Name of Previous Hospital	_____
Date of Admission to Previous Hospital	_____
Date of Intubation	_____

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FIVE STANDARD QUESTIONS

Instance	◯ ICU admission ◯ ICU discharge ◯ Hospital discharge
S5Q score	_____
Is the patient able to open and close their eyes, upon instruction?	◯ Yes ◯ No
Is the patient able to look at you when instructed?	◯ Yes ◯ No
Can the patient open their mouth and stick out their tongue, when instructed to?	◯ Yes ◯ No
Can the patient nod their head upon instruction?	◯ Yes ◯ No
Is the patient able to raise their eyebrows upon the count of five, after being instructed to do so?	◯ Yes ◯ No

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PAST MEDICAL HISTORY

Co-morbidities	☐ Hypertension ☐ Cholesterol ☐ Diabetes ☐ COPD ☐ Asthma ☐ Past TB ☐ Rheumatoid arthritis ☐ Ischemic heart disease ☐ Congestive cardiac failure ☐ Hypothyroidism ☐ Other
If other, please specify	_____
Smoking History	☐ Current ☐ Previous ☐ Ex-Smoker ☐ Never ☐ Other
Alcohol use:	☐ Yes ☐ No ☐ Unknown

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CURRENT MEDICAL HISTORY

Admission Category:	☐ Trauma ☐ Medical ☐ Surgery
If surgery:	☐ Elective ☐ Emergency
If trauma, please specify category:	☐ Upper limb fractures ☐ Lower limb fractures ☐ Spinal fractures ☐ Rib fractures ☐ Abdominal trauma ☐ Other
If surgical, please specify:	☐ Neurosurgery ☐ Abdominal surgery ☐ Vascular surgery ☐ Plastic surgery ☐ Other
If medical, please specify a category:	☐ COPD ☐ Asthma ☐ Cardiac Arrest ☐ Sepsis ☐ Overdose ☐ Other
If other, please specify:	_____
SASP 3 score on admission:	_____
Bloods taken on admission:	☐ Yes ☐ No
Date of bloods:	_____
WCC (if available)	_____
CRP (if available)	_____
HGT	_____
Comments:	_____

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LENGTH OF STAY

Date and time of intubation: _____

Date and time of extubation: _____

Length of intubation: _____

Date of admission: _____

Date of discharge from ICU: _____

Length of ICU stay: _____

Date of discharge from hospital: _____

Length of hospital stay: _____

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DAILY ASSESSMENT

Date and time:	_____
Days/hours intubated:	_____
Mode of ventilation:	☐ BiPAP ☐ PC SIMV ☐ VC SIMV ☐ CPAP ☐ Other
If other, please specify:	
Vitals trend: *A variation of 20% of their vital signs (HR, BP, Sats, RR) will be seen as unstable*	☐ Stable ☐ Unstable
Temp (highest temp in the last 24 hours)	_____
Preset RR	_____
Recorded RR	_____
Has the patient had spontaneous breaths in the last 24 hours?	☐ Yes ☐ No
Blood results available (in the last 24 hours):	☐ Yes ☐ No
Date of bloods:	_____
WCC	_____
CRP	_____
HGT	_____
Blood pH:	_____
Is the patient sedated?	◯ Yes ◯ No
Type and dose of sedation:	_____

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Mode of the RASS scale for the last 24 hours:	☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0 ☐ -1 ☐ -2 ☐ -3 ☐ -4 ☐ -5
GCS	_____
Is the patient receiving corticosteroids?	◯ Yes ◯ No
If yes, please specify name and dosage:	_____
Is the patient receiving neuromuscular blocking agents?	◯ Yes ◯ No
If yes, please specify name and dosage:	_____
Is the patient receiving glucose control?	◯ Yes ◯ No
If yes, please specify name and dosage	_____

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ULTRASOUND

Instance	◯ Day 1 ◯ Day 2 ◯ Day 3 ◯ ICU discharge ◯ Hopsital discharge

Diaphragm

Date	_____
Diaphragm thickness during inspiration on first breath (mm)	_____
Diaphragm thickness during inspiration on second breath (mm)	_____
Diaphragm thickness during inspiration on third breath (mm)	_____
Average diaphragm thickness during inspiration (mm)	_____
Diaphragm thickness during expiration on first breath (mm)	_____
Diaphragm thickness during expiration on second breath (mm)	_____
Diaphragm thickness during expiration on third breath (mm)	_____
Average diaphragm thickness during expiration (mm)	_____
Diaphragm thickening fraction 1	_____

Quads

RF thickness 1	_____
RF thickness 2	_____
RF thickness 3	_____
Average RF thickness	_____

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RF echogenicity 1	_____
RF echogenicity 2	_____
RF echogenicity 3	_____
Average RF echogenicity	_____
VI Thickness 1	_____
VI Thickness 2	_____
VI Thickness 3	_____
Average VI Thickness	_____
VI Echogenicity 1	_____
VI Echogenicity 2	_____
VI Echogenicity 3	_____
Average VI Echogenicity	_____

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PERIPHERAL MUSCLE STRENGTH

Instance	◯ ICU discharge ◯ Hopsital discharge
Date	_____
MRC	
MRC-SS performed	◯ Yes ◯ No
MRC-SS total	_____
Shoulder abduction LEFT	_____
Shoulder abduction RIGHT	_____
Elbow flexion LEFT	_____
Elbow flexion RIGHT	_____
Wrist extension LEFT	_____
Wrist extension RIGHT	_____
Hip flexion LEFT	_____
Hip flexion RIGHT	_____
Knee extension LEFT	_____
Knee extension RIGHT	_____
Ankle dorsiflexion LEFT	_____
Ankle dorsiflexion RIGHT	_____
Comments	_____

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Dynamometry	
Instance	○ Hopsital discharge
Dominant UL	○ Left ○ Right
Dominant LL	○ Left ○ Right
Left knee extension 1	
Left knee extension 2	
Left knee extension 3	
Predicted	
% predicted	
Rigth knee extension 1	
Rigth knee extension 2	
Rigth knee extension 3	
Predicted	
% predicted	
Left Shoulder abduction 1	
Left Shoulder Abduction 2	
Left Shoulder Abduction 3	
Right Shoulder Abduction 1	
Right Shoulder Abduction 2	
Right Shoulder Abduction 3	

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RESPIRATORY MUSCLE STRENGTH AND ENDURANCE

Instance	◯ ICU discharge ◯ Hopsital discharge
Date and time of assessment	_____
First MIP	_____
Second MIP	_____
Third MIP	_____
Best maximal inspiratory pressure	_____

Endurance

Instance	◯ Hospital discharge
50% MIP	_____
Time completed	_____
Number of breaths	_____
Comments	_____

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PHYSICAL FUNCTION TESTS

Instance	◯ ICU Discharge ◯ Hospital Discharge
Date	_____
CPAx	
CPAx performed	◯ Yes ◯ No
Total CPAx score	_____
CPAx score - Respiratory function	_____
CPAx score - Cough	_____
CPAx score - Bed mobility	_____
CPAx score - Lying to sit	_____
CPAx score - Dynamic sitting	_____
CPAx score - Standing balance	_____
CPAx score - Sit to Stand	_____
CPAx score - Transfer	_____
CPAx score - stepping	_____
CPAx score - Grip Strength	_____
Hand grip strength 1	_____
Hand grip strength 2	_____
Hand grip strength 3	_____

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Grip Strength Average	_____

Barthel Index

Total Score Barthel Index:	_____
Instance	○ Hospital discharge ○ 3 months
Feeding	○ 0 ○ 5 ○ 10
Moving from a chair to the bed and return (includes sitting up in bed)	○ 0 ○ 5 ○ 10 ○ 15
Grooming (wash face, comb hair, shave, clean teeth)	○ 0 ○ 5
Getting on and off toilet (handling clothes, wipe, flush)	○ 0 ○ 5 ○ 10
Bathing self	○ 0 ○ 5
Walking on level surface (or if unable to walk, propel wheelchair) *score only if unable to walk	○ 0* ○ 5* ○ 10 ○ 15
Ascend and descend stairs	○ 0 ○ 5 ○ 10
Dressing (includes tying shoes, fastening fasteners)	○ 0 ○ 5 ○ 10
Controlling bowels	○ 0 ○ 5 ○ 10
Controlling bladder	○ 0 ○ 5 ○ 10
Comments on missing data, if applicable:	_____

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QUALITY OF LIFE MEASURES

Instance	○ Hopsital discharge ○ 3 Months

EQ5D

Total EQ-5D score:	_____
Mobility score	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
Self-care score	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
Usual Activity score	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
Pain score	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
Anxiety/Depression score	○ 1 ○ 2 ○ 3 ○ 4 ○ 5
VAS Score	_____

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SIX MINUTE WALK TEST

Instance	○ Hopsital discharge
Date of 6MWT (ymd)	_____
Time of the 6MWT	_____
Medication (type & time issued)	_____
Use of a walking aid	○ Yes ○ No
If yes, please specify	_____
6MWT1 distance	_____
Pre 6MWT1 saturation	_____
Pre 6MWT1 HR	_____
Pre 6MWT1 Borg breathlessness	_____
Post 6MWT saturation	_____
post 6MWT1 HR	_____
post 6MWT1 Borg breathlessness	_____
post 6MWT1 Borg RPE	_____
6MWT comments	_____
6MWT2 Time	_____
6MWT2 distance	_____

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Pre 6MWT2 saturation	
Pre 6MWT2 HR	
Pre 6MWT2 Borg breathlessness	
Post 6MWT saturation	
post 6MWT2 HR	
post 6MWT2 Borg breathlessness	
post 6MWT2 Borg RPE	
6MWT comments	
Best 6MWT distance	
Expected 6MWT distance	
Percentage of normal	

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RETURN TO WORK

Have you returned to work?	◯ Yes ◯ No
If, yes:	◯ Are you doing the same work ◯ Light Duty ◯ Other
If other, please specify:	_____

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HEALTH CARE UTILIZATION

Where did you go when discharged from hospital?	◯ Home ◯ Step Down Facility ◯ Rehabilitation Centre ◯ Other
If other, please specify:	_____
Have you been admitted to hospital since your discharge from hospital?	◯ Yes ◯ No
Have you needed physical rehabilitation since your discharge from hospital?	◯ Yes ◯ No
If yes, please specify type:	_____
If yes please specify duration of rehabilitation:	_____

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MORTALITY

Has the patient passed away?

- ○ Yes
- ○ No

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COMMENTS

Was the patient lost to follow up:	◯ Yes ◯ No
Instance	◯ ICU ◯ ICU DISCHARGE ◯ HOSP DISCHRGE
If yes, provide reason:	_____
Where you unable to complete a test?	◯ Yes ◯ No
If yes which test:	_____
Why were you unable to complete the test?	_____
Why were you unable to perform the test?	_____
Randomisation sequence of tests at ICU discharge:	_____
Randomisation sequence of tests at hospital discharge:	_____

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ADDENDUM I : Pilot Study

The pilot study was conducted prior to the commencement of the main study.

OBJECTIVES:

- To determine the intra-rater reliability of ultrasonography measurements
- To determine the inter-rater reliability of ultrasonography measurements
- To determine the intra-rater reliability of peripheral muscle strength by handheld dynamometry
- To determine the intra-rater reliability of respiratory muscle strength by measuring MIP of participants

METHODS:

Study setting: This pilot study was conducted in two settings. Ultrasonography measures were conducted in a public hospital in Cape Town, South Africa (SA). Peripheral and respiratory muscle strength measures were conducted in a private practice in Somerset West, Cape Town, SA.

Ethical considerations: All participants provided informed consent

Sample:
Ultrasonography: A sample of convenience; included seven critically ill adult individuals for measures of diaphragm thickness and five critically ill individuals for measures of peripheral muscle thickness and echogenicity.
Peripheral and respiratory muscle strength measures: A sample of convenience; included five healthy adult individuals.

Measurements

1. Ultrasonography

Procedure: The Primary Investigation (PI) scheduled three meetings with the expert ultrasonographer (EUS). At each instance the aims and objectives for ultrasonography measures were explained to each participant and informed consent was obtained. At the third meeting, intra-rater reliability and inter-rater reliability of ultrasound measurements were established. Peripheral muscle thickness (RF and VI) and echogenicity (see Table 1 and 2) as well as diaphragm thickness for both inspiration and expiration (see Table 3), were measured by the PI. Measurements were completed in the same order by the PI. The test setting and equipment set-up remained standardized and all equipment was calibrated prior to testing. The measures for ultrasonography of the diaphragm and quadriceps were performed as described in Section 3.11.1.1.

Intra-rater reliability: Ultrasounds measurements of the peripheral muscles and diaphragm were performed by the PI on the same day separated by a 30-minute interval, using the same ultrasound equipment with the participant in a relaxed, supine position. PI measurements were compared to establish intra-rater reliability.

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Inter-rater reliability: Ultrasound measurements of the peripheral muscles and diaphragm were performed by the EUS on the same day separated by a 30-minute interval, using the same ultrasound equipment with the participant in a relaxed, supine position. PI and EUS measurements of peripheral muscles and diaphragm thickness were compared to establish inter-rater reliability.

Table 1: Intra-rater and inter-rater reliability of quadriceps thickness measurements

RF								
US 1	US 2	US 3	**EUS: mean**	PI 1	PI 2	PI 3	**PI: mean**	**PI: mean 2**
1,046	1,059	1,059	**1,055**	1,132	1,138	1,159	**1,143**	**1,269**
0,509	0,489	0,523	**0,507**	0,448	0,523	0,502	**0,491**	**0,586**
0,325	0,325	0,346	**0,332**	0,36	0,34	0,34	**0,347**	**0,333**
0,523	0,516	0,523	**0,521**	0,53	0,557	0,577	**0,555**	**0,502**
0,712	0,718	0,732	**0,721**	0,908	0,874	0,935	**0,906**	**1,272**
VI								
0,693	0,686	0,679	**0,686**	0,671	0,671	0,665	**0,669**	**0,89**
0,577	0,577	0,55	**0,568**	0,428	0,435	0,462	**0,442**	**0,453**
0,237	0,244	0,264	**0,248**	0,251	0,25	0,258	**0,253**	**0,310**
0,374	0,381	0,401	**0,385**	0,401	0,394	0,435	**0,41**	**0,448**
0,718	0,725	0,725	**0,723**	0,739	0,745	0,739	**0,741**	**0,903**

*RF= Rectusfemoris; VI= Vastusintermedius; EUS=expert ultrasonographer; PI= primary investigator; mean = instance 1; mean 2 = instance 2

Table 2: Intra-rater and inter-rater reliability quadriceps echogenicity measurements

Echogenicity measures			
RF	**EUS**	**PI 1**	**PI 2**
	75	73	79
	99	95	92
	57	57	64
	79	64	65
	108	102	107
VI			
	62	59	62
	42	39	36
	28	38	30
	40	30	43
	72	45	75

*EUS=expert ultrasonographer; PI= primary investigator; PI 1 = instance 1; PI 2 = instance 2

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Table 3: Intra-rater and inter-rater reliability of diaphragm thickness measurements

Inspiration								
US 1	US 2	US 3	**EUS: mean**	PI 1	PI 2	PI 3	**PI: mean**	**PI: mean 2**
0,356	0,341	0,371	**0,356**	0,249	0,223	0,238	**0,236**	**0,126**
0,204	0,216	0,245	**0,221**	0,2	0,212	0,208	**0,207**	**0,198**
0,516	0,269	0,294	**0,360**	0,282	0,282	0,274	**0,280**	**0,432**
0,218	0,244	0,237	**0,233**	0,233	0,207	0,226	**0,222**	**0,242**
0,344	0,344	0,37	**0,353**	0,237	0,226	0,248	**0,237**	**0,201**
0,255	0,229	0,243	**0,242**	0,328	0,325	0,321	**0,325**	**0,343**
0,277	0,299	0,325	**0,300**	0,314	0,31	0,310	**0,311**	**0,364**
Expiration								
0,307	0,329	0,333	**0,323**	0,204	0,172	0,216	**0,197**	**0,109**
0,171	0,197	0,178	**0,182**	0,171	0,186	0,178	**0,178**	**0,168**
0,264	0,264	0,267	**0,265**	0,253	0,256	0,263	**0,257**	**0,4**
0,189	0,207	0,196	**0,198**	0,192	0,207	0,196	**0,199**	**0,212**
0,314	0,314	0,314	**0,314**	0,211	0,2	0,211	**0,207**	**0,163**
0,192	0,195	0,221	**0,203**	0,277	0,270	0,255	**0,267**	**0,311**
0,251	0,266	0,288	**0,268**	0,281	0,288	0,278	**0,282**	**0,319**

*EUS=expert ultrasonographer; PI= primary investigator; mean = instance 1; mean 2 = instance 2

2. Peripheral and respiratory muscle strength testing

Procedure: The PI scheduled one session with participants. At this session the aims and objectives for peripheral and respiratory muscle strength testing were again explained and informed consent obtained. Mouth pressure manometer measurements for diaphragmatic strength (see Section 3.11.1.3) and handheld dynamometry measurements for peripheral muscle strength (see Section 3.11.1.2) were completed. All baseline measurements (height, weight and age) were recorded (Refer to Table 4).

Table 4: Demographics of handheld dynamometry and manometer measure participants

Participant code	**Gender**	**Age**	**Weight (kg)**	**Height (m)**
1	female	24	66kg	1,7
2	female	64	60kg	1,57
3	female	26	66kg	1,68
4	female	25	48kg	1,58
5	female	61	64kg	1,64

Intra-rater reliability: Handheld dynamometry and manometer measurements were performed by the PI on the same day separated by a fifteen-minute interval, using the same equipment with the participant seated. PI measurements were compared to establish intra-rater reliability

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Table 5: Intra-rater reliability of manometer measurements

Instance 1				Instance 2			
MIP 1	MIP 2	MIP 3	**Best MIP**	MIP1	MIP 2	MIP 3	**Best MIP**
127	133	132	**133**	117	126	112	**126**
52	47	47	**52**	52	48	49	**52**
90	92	92	**92**	88	83	90	**90**
78	75	72	**78**	73	70	65	**73**
65	70	65	**70**	71	73	65	**73**

MIP= maximal inspiratory pressure

Table 6: Intra-rater reliability of handheld dynamometry measurements

Instance 1 Left quadriceps				Instance 2 Left quadriceps			
HHD 1	HHD 2	HHD 3	**Best HHD**	HHD1	HHD 2	HHD 3	**Best HHD**
208,6	206,8	219,3	**219,3**	208,2	189,9	191,3	**208,2**
189	196,6	193,5	**196,6**	199,7	191,3	196,6	**199,7**
160,6	147,7	143,2	**160,6**	144,1	167,7	153,4	**167,7**
197,1	185,5	198,4	**198,4**	206,8	209,5	193,5	**209,5**
223,3	220,6	222,4	**223,3**	225,1	229,1	223,7	**229,1**

Instance 1 Right quadriceps				Instance 2 Right quadriceps			
HHD 1	HHD 2	HHD 3	**Best HHD**	HHD1	HHD 2	HHD 3	**Best HHD**
228,6	212,2	214	**228,6**	190,8	198,8	208,6	**208,2**
161,5	173	167,2	**173**	170,8	159,7	168,6	**170,8**
150,8	165	156,6	**165**	172,6	203,3	189,5	**203,3**
222,9	241,1	224,2	**241,1**	230,9	218,8	215,3	**230,9**
207,7	207,3	200,6	**207,7**	224,6	208,6	226	**226**

HHD= handheld dynamometry

Data analysis: Intra Class Correlation for average measures with a 95% confidence interval (CI) was used to determine intra- and inter-rater reliability. An ICC value of ≥0.70 was regarded as excellent reliability.

RESULTS

1. Ultrasonography

The ICC for measures of RF muscle thickness and echogenicity was 0,97 (0,87 - 0,99) between the measures of the EUS and PI and an ICC of 0,95 (0,56 - 0,99) between average measures of the RF muscle by the PI. The ICC for measures of VI muscle thickness and echogenicity was 0,97 (0,88 - 0,99) between measures of the EUS and PI. An ICC of 0,96 (0,66 - 0,99) between average measures of the VI muscle by the PI.

The ICC for inspiration was 0,80 (0,37-0,94) and an ICC of 0,80 (0,39-0,94) for expiration between the EUS and PI. For the PI the ICC for inspiration was 0,70 (-2,40-0,96) and 0,74 (-0,68-0,96) for expiration.

2. Peripheral and respiratory muscle strength testing

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For MIP an ICC of 0,99 (0,99-1,00) was seen for the PI. The ICC of the R quadriceps was 0,83 (-0,95-0,98) and the ICC was 0,97 (0,76-0,99) for the L quadriceps.

CONCLUSION

Excellent intra- and inter- rater reliability was achieved for ultrasonography measures of the diaphragm and quadriceps (RF and VI muscles). Excellent intra-rater reliability was also achieved for measures of peripheral and respiratory muscle strength.

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ADDENDUM J : Abstract presented at CCNC

Physical Function Outcomes of Privately Admitted Intensive Care Unit Patients at Hospital Discharge

Authors & Affiliations: Pool. HA1, Lupton-Smith. A1, Hanekom. SD1

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Background: Poor physical function following critical illness is a major contributor to morbidity in survivors. Physical function has not been described within the Private Health population in South Africa.
Objective: To describe muscle strength, physical function and exercise capacity in critical illness survivors at intensive care unit (ICU) and hospital discharge.
Materials and methods: Prospective observational cohort study was conducted in the ICU's of a Private Hospital in the Western Cape.
Results: Preliminary results of 16 participants (8 male) with a mean age of 68.19 years (SD 15.58) are presented. The mean severity of illness score (SAPS 3) was 59.13 (SD 15.47). The median length of ventilation was 5.78 (IQR 3.93 – 9.67) days, mean total length of stay was 13.38 (SD 7.85) days in ICU and 19.06 (SD 11.1) days in hospital. Mean Medical Research Council sum score (MRC SS) was 47.82 (SD 8.13) at ICU discharge and median MRC SS of 53.00 (IQR 40 – 56) at hospital discharge. Walking distance (exercise capacity) was a median of 117 (IQR 87 – 120) meters. Mean physical function scores were 36.91 (SD 6.06) at ICU discharge and 41.80 (SD 5.47) at hospital discharge using the Chelsea Critical Care Assessment tool (CPAx).
Conclusion: Critical illness survivors demonstrated impaired physical function outcomes.

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From: **Critical Care National Congress Registration Team** criticalcare@allevents.co.za
Subject: Acceptance of abstract for oral presentations
Date: 19 August 2019 at 13:44
To: Helena (Helanie) Pool poolhelanie@yahoo.com

Aug 19, 2019

Dear Helena (Helanie) Pool,

This serves to confirm your abstract has been accepted for an ***oral presentation*** for the Critical Care SASPEN Congress, 28 August – 1 September 2019.

Speaker Presentations

Title	Physical Function Outcomes of Privately Admitted Intensive Care Unit Patients at Hospital Discharge
Paper Status	Accepted
Presentation Type	Oral
Theme	Critical Care
Presenting Author	Miss Helena (Helanie) Pool Affiliations: University of Stellenbosch

Please ensure your presentation does not exceed 8 minutes with a 2 minute for Q&A and that the aspect ratio for the presentation is set to 16:9. See below instruction on where to check this in powerpoint:

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